Cleveland Clinic Quarterly

A Bulletin Published by
The Staff of the Cleveland Clinic
CLEVELAND, OHIO

Vol. 7 July, 1940 No. 3

CONTENTS

CLEVELAND CLINIC QUARTERLY

Issued in four numbers during the year; one in January, one in April, one in July and one in October, by Cleveland Clinic Foundation, 2020 East 93rd Street, Cleveland, Ohio.

Entered as second-class matter March 4, 1935, at the Post Office at Cleveland, Ohio, under the Act of August 24, 1912.

CELIAC GANGLIONECTOMY FOR RAYNAUD'S DISEASE

Further Report of a Case Operated on Three Years Ago

GEORGE CRILE, M.D.

Three years ago (July, 1937) I reported in this journal[1] the immediate results of bilateral celiac ganglionectomy for a case of Raynaud's disease. The patient was a forty-two year old male who had had pain in the fingers and toes for fifteen years. He also had had intermittent numbness and tingling in the fingers, with the symptoms becoming progressive in nature so that he had been unable to work for five years. For three and a half years he had had paroxysmal pain in the finger tips which were very sensitive to pressure. This pain was so severe that he had become addicted to morphine for relief. There was a loss of sensation in the hands and feet and even in hot weather the fingers were ice cold. Typical gangrene developed in the fingers, necessitating the amputation of the right middle finger in 1934 and the left middle finger in 1937, three months before he was first seen at the Clinic (Fig. 1).

A left celiac ganglionectomy was performed on May 3, 1937 and a right celiac ganglionectomy on May 17, 1937. Complete relief from the symptoms of Raynaud's disease occurred almost simultaneously with the completion of the first operation. The patient has returned at intervals for check-ups, and was examined here on April 11, 1940. At this

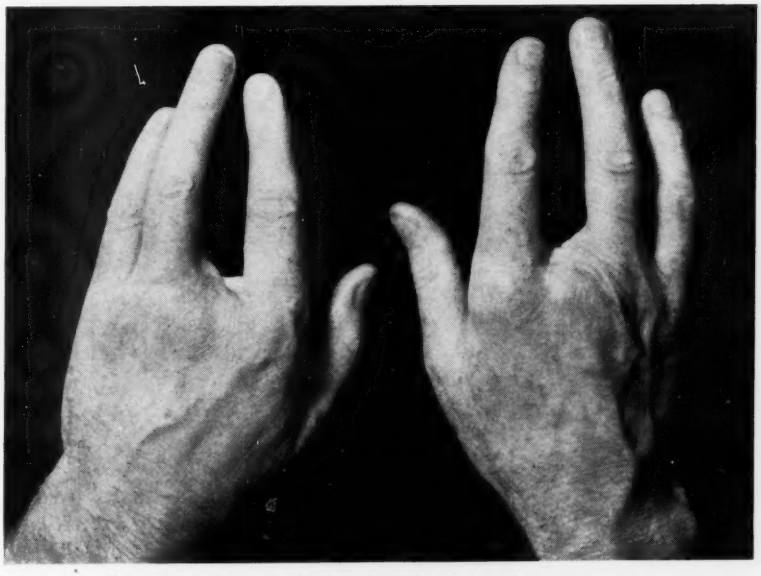


FIGURE 1: Photograph of patient's hands showing amputations.

time he stated that since the operations he no longer felt any pain nor any sensation of coldness in the extremities. A complete physical examination revealed the patient to be in good physical condition with normal radial pulsations, normal skin texture and a warm dry skin.

Dr. W. J. Zeiter, who measured the skin temperatures, reports that readings taken at the time of this recent follow-up continued to be two degrees higher than the average when the patient was first seen, indicative of the return of normal circulation to the extremities.

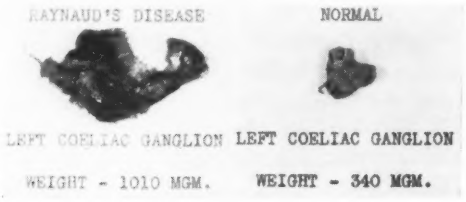


FIGURE 2: Celiac ganglion in case of Raynaud's disease compared with normal.

In the previous article we reported the abnormal size of the celiac ganglia in this case (Fig. 2): left, 1010 mg., and right, 535 mg. (normal being 340 mg.). This large size of the ganglia, which is comparable to the size in many cases of hypertension (Fig. 3), when considered together

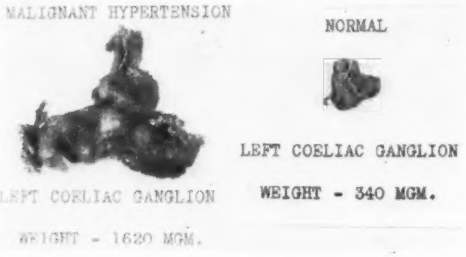


FIGURE 3: Celiac ganglion in case of essential hypertension compared with normal.

with the results of their removal, suggest that Raynaud's disease as well as hypertension is due to a pathologic physiology of the celiac ganglia, the size of which appears to be an inherited characteristic.

The personality background of this patient who suffered from Raynaud's disease is also similar to the personality background of the patient afflicted with hypertension. At school he made a good scholastic record, was active and tireless and engaged in strenuous athletics, for six years being a professional boxer. This individual history closely parallels that of the typical hypertensive history, in which a good scholastic record, an interest in athletic activities, and an active and tireless personality go hand in hand with the equipment which predisposes to hypertension and, similarly, to Raynaud's disease.

The results in this case, which have now continued for more than three years, and the fact that ganglionic tissue cannot be regenerated indicate that the celiac ganglion is the logical point of attack in the treatment of Raynaud's disease.

Reference

1. Crile, G.: A case illustrating the analogy between essential hypertension and Raynaud's and Buerger's disease, Cleveland Clin. Quart., 4:184-186, (July) 1937.

TREATMENT OF POLYCYTHEMIA VERA

RUSSELL L. HADEN, M.D.

Polycythemia vera is characterized by an increase in the number of red blood cells. This disease is insidious in origin, chronic, and without pathognomonic symptoms or physical findings. Early in the disease and in mild cases there may be no detectable abnormality on physical examination. In well advanced cases the spleen usually is enlarged, the mucous membranes are injected, and the patient is cyanotic or rather a raspberry-red color. The enlargement of the spleen results from the excess storage of red cells; the injection and cyanosis depend on the slowed circulatory rate resulting from the high viscosity of the blood.

On physical examination or laboratory study, the one constant finding in polycythemia vera is the high red cell count. In erythrocytosis the erythrocyte count is high also. Here, however, the total blood volume is not increased. In polycythemia vera the total blood volume as well as the red cell count is constantly high. This increase occurs in symptomatic polycythemia vera as well as in the idiopathic type.

The determination of the blood volume thus becomes a valuable aid in differentiating erythrocytosis and polycythemia vera. The increase in blood volume is due entirely to the increase in the red cells so the most valuable indicator of the increase is the red cell mass per kilogram of body weight[1]. The mean mass of red cells in normal men is 30 cc. and in women 26.4 cc. per kilogram. While this figure is not increased in erythrocytosis, although the red cell count may be high, it is always increased in polycythemia vera and may be increased even to five times its normal volume.

A classification of polycythemia with the more important causes for the high red cell count is given in Table 1. In our laboratory the blood

TABLE 1

CLASSIFICATION OF POLYCYTHEMIA

I. Erythrocytosis (secondary or simple polycythemia)
   Increase in number of erythrocytes without increase in red cell mass per kilogram
II. Polycythemia vera or erythremia
   Increase in number of erythrocytes with increase in red cell mass per kilogram
   A. Symptomatic polycythemia vera due to
      1. Low barometric pressure
      2. Impaired oxygenation in lungs from:
         a. Bypassing of lungs in congenital heart disease
         b. Decreased aerating surface by lung disease
      3. Impaired capacity of hemoglobin to carry oxygen as in methemoglobinemia
   B. Idiopathic polycythemia vera from unknown cause

volume is determined by the method of Rowntree, Brown and Roth[2]. The total red cell mass is calculated from the hematocrit reading and the total blood volume.

Erythrocytosis is simply treated by an occasional venesection or may need no treatment at all. In polycythemia vera, however, treatment is always required since the symptoms of headache, dizziness, and weakness depend upon the high viscosity which can be lowered only by decreasing the number of red cells. The vascular symptoms can be helped only by removing the excess of cells.

Polycythemia vera has been treated both from the standpoint of destroying the excess cells and from preventing the formation of the excess. Acetylphenylhydrazine is the drug of choice in destroying the excess cells. It is less toxic than phenylhydrazine and less toxic than benzol which also has been used. Patients vary greatly in the sensitivity to the drug, both from the standpoint of toxic effect and hemolytic action. Some patients can take large amounts with little destruction of cells; others will develop a skin rash, fever, nausea, vomiting, and liver disturbances from small doses. With such a great variation in effect, the use of the drug is very unsatisfactory in most cases. If the drug is effective, the red cells may be destroyed at a very rapid rate so the amount of blood destruction cannot be controlled. The bone marrow usually responds rapidly to such a hemolytic anemia with a high reticulocyte count, which indicates rapid red cell regeneration. All the materials, especially iron, needed for red cell formation are still present so the new cells are formed rapidly. In an occasional patient the drug will have just the desired effect so the level of red cells is well controlled. Thus one patient treated himself satisfactorily for over ten years with small doses, using the color of his nose as the criterion for dosage.

With the hemolytic anemia produced by acetylphenylhydrazine, the cells are larger than normal so the red cell mass which is primarily treated is larger than normal for the number of cells instead of smaller as in an iron deficiency anemia.

If acetylphenylhydrazine is to be tried, 0.1 gram is given daily for ten days unless contraindications arise. The hemolysis may continue after the drug is withdrawn so if daily counts show evidence of rapid cell destruction, the drug should be discontinued at once. It is desirable to work out a regular dosage after the initial course. One dose of 0.1 gram weekly may be sufficient.

Irradiation of the spleen and long bones has been employed often. In the patients we have treated and in cases observed so treated elsewhere, there has been little beneficial effect from such treatment. Irradiation may have some place as an adjunct in treatment. It is valuable when the spleen is very large from coincidental myeloid hyperplasia.

The most satisfactory method of treatment is venesection. If sufficient

blood is removed, an iron deficiency is produced, thus preventing the formation of cells. With an iron deficiency, the cells decrease in volume so the red cell mass is small for the number of cells instead of large as with a hemolytic anemia due to acetylphenylhydrazine. All patients respond to this method of treatment and all toxic reactions are avoided.

In treatment by venesection, it is most important to remove a sufficient quantity of blood. The excess of red cells should be completely removed if no contraindications arise. In this way the regeneration of cells will be very slow. It is very poor therapy to remove only small portions at a time. This may even stimulate blood formation rather than retard it. The total red cell mass is calculated first from the total blood volume and the hematocrit reading. Knowing the normal red cell mass for the patient, it is easy to calculate the amount of blood to be removed. An illustrative calculation is as follows:

Male patient—weight 70 Kg.

The hematocrit reading shows 60 cc. of cells per 100 cc. of blood and the total blood volume is 8,000 cc.

Red cell mass $= 8{,}000 \times 60 =$	4,800 cc.
Normal for patient $= 70 \times 30 =$	2,100 cc.
Excess cells	2,700 cc.

As blood is withdrawn, the hematocrit reading will fall to the normal value of 45 cc. The mean will be about 52 cc. The amount of whole blood to be removed is $\frac{2{,}700}{52} \times 100 = 5{,}200$ cc. As the blood is withdrawn, a balance sheet is kept to determine the exact result of the treatment (Table 2). If the red cell mass is exceedingly high, it may not be possible to reduce the red cell mass to normal during the first course of treatment. This one patient recently had a red cell mass of 9,096 cc. when the normal for his weight was 2,100 cc. Nearly 7,000 cc. of blood was removed during a week and the red cell mass was still almost twice too high. This was reduced to normal by more venesections later.

After the red cell mass is reduced to normal by venesection, the regeneration of blood is very slow, seemingly due to the iron deficiency. Patients vary in the rate of regeneration but usually venesections are required only at intervals of six to twelve months. The mean cell volume remains low due to the iron deficiency (Table 3).

All patients in our series are now being treated by venesection. If the spleen is very large and the leukocyte count high, especially if myelocytes appear, irradiation of the spleen and marrow is utilized also. An occasional patient is taking some acetylphenylhydrazine where this treatment has been found satisfactory and no toxic effects have developed. The effect of the bleeding on the blood findings is shown in Table 3.

A detailed history of one patient observed for the past twelve years illustrates the many phases of idiopathic polycythemia vera, the chronic course, and the response to treatment.

TABLE 2

RED CELL MASS BALANCE SHEET

8/31/39	*Red cell mass (blood volume x hematocrit reading)*	*3,464 cc. (67 cc. per Kg.)*		
		Blood removed cc.	*Hematocrit reading cc.*	*Red cells removed*
	9/11/39 Venesection	600	67	402
	9/12/39 "	700	63	441
	9/13/39 "	750	54	405
	9/14/39 "	725	49	355
		2,775 cc.		1,603 cc.
9/5/39	Red cell mass — 1,675 cc. (32 cc. per Kg.) Calculated cells removed — 1,789 cc.			
11/10/39	Red cell mass — 1,926 cc. (34 cc. per Kg.)			
2/16/40	Red cell mass — 2,030 cc. (36 cc. per Kg.)			

Case Report

Case 1: This patient, a merchant thirty-seven years of age, was first seen in 1928, complaining of pain in the right foot which had been present for three months. The toes became red and painful but were not swollen. He had tried various measures such as arch supports without relief. The general examination was negative and no definite cause for the symptoms was found. At that time the red cell count was recorded as 4,780,000 and the hemoglobin as 85 per cent. The leukocyte count, however, was 16,300. No explanation for the leukocytosis was given. It is evident that this was due to polycythemia in view of the later developments.

The patient was not seen again until 1934, when he returned complaining of pain and swelling of the middle toe of both feet. Three weeks before admission blisters had appeared on the right middle toe. The foot became swollen and red. The toe was incised but no pus was obtained. He was now having similar symptoms on the same toe of the left foot. The toes were painful. He had large varicose veins. In an orthopedic examination it was noted that both feet were livid and that a fungus infection was present. The clinical diagnosis was vascular disease of both feet and epidermophytosis. The spleen was not palpable.

A blood count now, however, showed 6,290,000 red cells and 117 per cent hemoglobin. The leukocytosis observed six years previously was still present (white blood count 12,600). A blood volume study two weeks later showed 56 cc. of red cells per kilogram of body weight, (Normal, 30 cc.). The red cell count was now 7,100,000.

The administration of acetylphenylhydrazine was begun and a total of 2 gm. of the drug in 0.1 gm. doses was taken. The patient returned one week later complaining of retrosternal discomfort, burning in the epigastrium, and food distress. The icterus index was 10 units, the leukocyte count 16,800. and the red cell count was about the same. Three weeks later the congestion of the conjunctiva previously noted and the pain in the feet had decreased. The red cell count had fallen to 4,730,000 and the hemoglobin to 81 per cent. The leukocyte count was 18,600. The reticulocyte count was 3.5 per cent, indicating a rapid regeneration of cells. Two weeks later the blood count was much the same and the red cell mass was 28 cc. Two months later the red cell count and cell mass were again high so acetylphenylhydrazine was again given. This time the medication was not well tolerated and the patient developed fever, chills, and vomiting. The medicine was discontinued.

The patient was not observed again until ten months later when the red cell count was 6,950,000, the hemoglobin was 111 per cent, and the white count was 19,100. The total red cell mass was 50 cc. The use of acetylphenylhydrazine was advised but was not taken because of the previous experience with unpleasant reactions.

Fifteen months later the patient began to feel dull, listless, and dizzy. He had had a marked redness of one eye for the preceding week. The red cell count was now 7,010,000, the hemoglobin 111 per cent, and the total red cell mass 55 cc. per Kg.

The patient was next seen two months later at his home with his local physician. He stated that following a single dose (0.1 gm.) of acetylphenylhydrazine, fever, jaundice, and malaise developed. The leukocyte count was 18,000. There was tenderness over the gall bladder; the conjunctivae were icteric. An acute cholecystitis was suspected and operation was advised. On examination there was marked congestion of the conjunctivae and the lips were livid. The viscosity was 9.2 units. The findings suggested that the symptoms were secondary to the

TABLE 3

EFFECT OF BLEEDING ON NUMBER, SIZE AND SHAPE OF RED CELL

	Red cell count	*Red cell mass per Kg.*	*Volume index*	*Color index*	*Diameter*	*Thickness*
	millions	*cc.*			*microns*	*microns*
1. Before	7.75	67	0.96	0.77	7.6	1.90
After	7.72	36	0.77	0.65	7.6	1.55
2. Before	9.01	79	0.78	0.62	7.2	1.75
After	5.60	37	1.78	0.58	7.2	1.75
3. Before	8.33	88	0.97	0.74	7.5	2.00
After	8.38	44	0.77	0.62	7.0	1.85
4. Before	9.42	134	0.92	0.78	7.6	1.80
After	8.56	60	0.73	0.61	7.4	1.80
5. Before	9.55	99	0.91	0.82	7.2	2.00
After	8.04	38	0.69	0.54	7.2	1.60

high viscosity. The red cell count was 6,750,000. Following venesection and the use of physiologic sodium chloride solution intravenously all the symptoms cleared up quickly.

It was evident that this patient should be given no more acetylphenylhydrazine so bleeding was continued. Several venesections were done during the next six months.

During the past two years venesection has been done more frequently. One year ago four venesections were done to bring the blood to a normal level as follows:

Total red cell mass before treatment		3,838 cc.
Cells removed—first venesection	348 cc.	
Cells removed—second venesection	280 cc.	
Cells removed—third venesection	270 cc.	
Cells removed—fourth venesection	260 cc.	
Total removed	1,158 cc.	
Total red cell mass after treatment		2,733 cc.
Difference		1,105 cc.

During the next eleven months, only 1,200 cc. of blood were removed. A blood study at this time showed a total red cell mass of only 52 cc. The conjunctivae were again injected. The spleen still was not palpable. The patient was having few symptoms. The red cell count was 7,920,000 and the white cell count was 17,650. The patient was again bled as follows:

Total cell volume before bleeding		4,062 cc.
Cells removed—first venesection	482 cc.	
Cells removed—second venesection	482 cc.	
Cells removed—third venesection	450 cc.	
Cells removed—fourth venesection	384 cc.	
Total removed	1,798 cc.	
Total cell volume after bleeding		2,204 cc.
Difference		1,858 cc.

The actual number of cc. of cells removed (1,798 cc.) checks closely with the calculated amount (1,858 cc.). The red cell mass was now normal. Bleeding probably will not be necessary again for several months. The red cell mass in relation to treatment is shown in figure 1.

Comment: This patient is free of symptoms since the last treatment. He is very interesting and illustrates the chronic course of the disease and good control in bleeding. The leukocytosis and vascular disease were the first manifestations of any abnormality. The nature of the disease was not recognized early in its course. He was very sensitive to acetylphenylhydrazine as shown by the severe toxic symptoms with small doses and the exaggerated hemolytic response to the drug. The spleen

has never been palpable. The disease, when properly treated, has not interfered with normal activity. The vascular symptoms have not progressed.

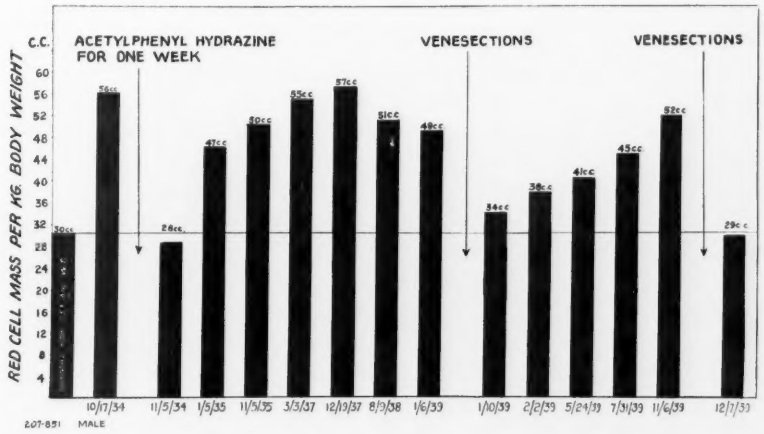


FIGURE 1: (Case 1): The red cell mass per Kg. of patient reported. Note the large mass before treatment. This fell to a point below normal with the administration of acetylphenylhydrazine but quickly rose again. The increase after venesection is very slow.

REFERENCES

1. Haden, R. L.: The red cell mass in polycythemia in relation to diagnosis and treatment, Am. J. M. Sc., 196:493-502, (October) 1938.
2. Rowntree, L. G., Brown, S. E., and Roth, S. M.: The Value of the Blood and Plasma in Health and Disease, W. B. Saunders Co., Philadelphia, 1929.

PENTOTHAL SODIUM ANESTHESIA IN PNEUMO-ENCEPHALOGRAPHY

A Preliminary Report

W. JAMES GARDNER, M.D., WM. A. NOSIK, M.D., and ROBERT E. BRUBAKER, M.D.

In view of the increasing application of intravenous anesthetics to general surgical operations, and of the favorable reports of their use in some neurosurgical procedures [1, 2], a series of pneumo-encephalograms, employing pentothal sodium, has been done. In a series of twenty-five consecutive cases, pentothal sodium anesthesia has proved to be well adapted to this procedure from the standpoint of the patient, the anesthetist, and the operator.

PROCEDURE

A hypodermic injection of morphine sulfate, grains 1/6, and atropine sulfate, grains 1/150, is given forty-five minutes preoperatively. The patient is taken to the encephalography room, secured in the operating chair, and the field prepared and draped. The lumbar interspace selected for the subsequent introduction of the encephalogram needle is then infiltrated with 0.75 per cent novocaine. This pre-anesthetic infiltration allows a smoother and lighter anesthesia as the stimulation from the insertion of the needle is avoided.

A suitable vein in the arm or hand is selected for the injection of the anesthetic. The needle is connected with a two-way stopcock, one inlet of which receives the pentothal solution, and the other a drip of normal saline which continuously clears blood from the needle between the intermittent injections of the anesthetic. After the induction of anesthesia, the encephalogram needle is inserted into the lumbar interspace which already has been infiltrated with novocaine, and the exchange of cerebrospinal fluid and air is completed. The injection of the anesthetic then is discontinued and roentgenograms are taken immediately. The induction of anesthesia is carried out with the patient sitting in the operating chair. Figure 1 shows the set-up for the procedure and the administration of the anesthetic.

CLINICAL DATA

The twenty-five patients presented were from fourteen to fifty-eight years of age. Eighteen patients were in the third and fourth decades.

The post-encephalographic diagnoses were: grand mal, ten cases; post-traumatic encephalopathy, four cases; brain tumor, three cases; unverified brain tumor, two cases; major hysteria, three cases; and one case each of cerebral scar, cerebral vascular disease, and Alzheimer's disease.

The amount of pentothal sodium injected as a 5 per cent solution varied from 0.22 gram to 1.5 grams, the average being 0.7 gram.

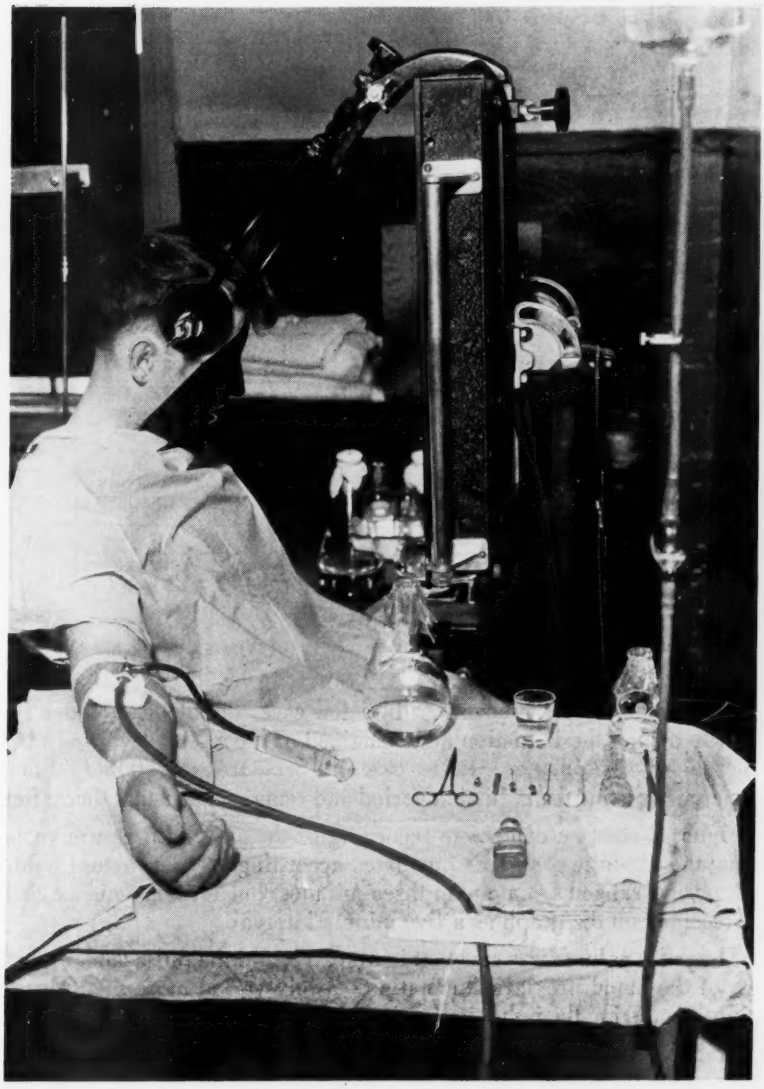


FIGURE 1. Set-up for the procedure and the administration of the anesthetic.

The blood pressure charts of the majority of the patients showed a characteristic curve. During induction of the anesthesia, both systolic and diastolic pressures fell 5 to 25 mm. of mercury. However, at the beginning of the procedure or during its course the pressures rose to the

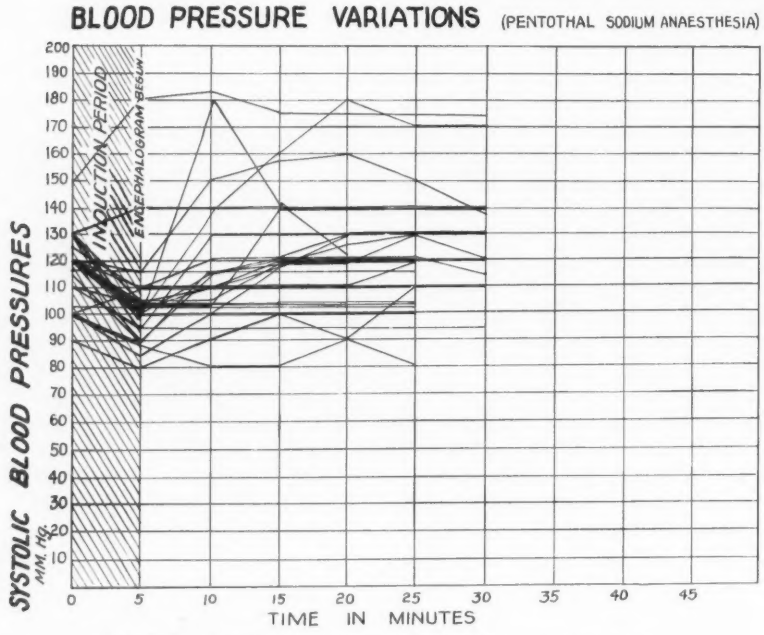


FIGURE 2: Composite recording of the systolic pressure variations.

pre-anesthetic level or above it. In a few cases the blood pressure fell slightly during the induction and remained at a constant level. In two cases there was no change. In two cases the pressure rose 10 and 30 mm. of mercury during the induction period and remained constant thereafter.

Figure 2 shows a composite recording of the systolic pressure variations; the diastolic pressures fluctuated accordingly. The actual induction period ranged from one to three minutes, but for convenience, it is represented on the graph as a five minute interval.

The pulse volume was constant in all cases, and the pulse rate, regardless of the blood pressure fluctuations, rarely varied more than plus or minus ten during the induction period and the subsequent procedure.

Marked respiratory depression was not noted, the rate of injection of the pentothal sodium solution being carefully regulated to prevent this occurrence. Pallor appeared in one case, but no other untoward anesthetic effects resulted.

The recovery period and convalescence were uneventful in each instance. Nausea and vomiting occurred in one case, but in the remaining twenty-four cases the postanesthetic course was quiet and comfortable. It is our impression that post-encephalographic headache after the

use of pentothal sodium anesthesia is distinctly less annoying to the patient than after the use of other agents.

Conclusions

Pentothal sodium satisfies the desiderata of anesthesia in pneumoencephalography—a smooth induction period, minimal changes in blood pressure, pulse, and respirations due to the anesthetic itself, and a quiet recovery period. We believe that its continued use in this procedure is justified when no contraindications to the type of anesthesia exist.

References

1. Tuohy, E. B.: Anesthetic procedures used at the Mayo Clinic. II. For neurologic surgery, Proc. Staff. Meet. Mayo Clin., 13:377-379, (June 15) 1938.
2. Ruth, H. S., Tovell, R. M., Milligan, A. D. and Charleroy, D. K.: Pentothal sodium: Is its growing popularity justified? J. A. M. A., 113:1864-1868, (November 18) 1939.

IDIOPATHIC SPONTANEOUS PNEUMOTHORAX

H. SCOTT VAN ORDSTRAND, M.D.

In the minds of the medical profession, the diagnosis of pneumothorax too often infers the stigmata of tuberculosis in spite of increasing reports of numerous non-tuberculous cases, many without proved etiology. The association of tuberculosis with pneumothorax undoubtedly arises from its relative frequency in sanatoriums. Pneumothorax rarely occurs in the early stages of clinical tuberculosis, and if present, it is a late complication. In general medical practice, it is encountered in many non-tuberculous diseases as a complication of such entities as pure silicosis, asthma, pneumonia, lung abscess, lung tumor, etc. It has been reported following the administration of lipiodol, and one writer has emphasized its familial tendency in a few cases.

Although we have known for over fifty years that pneumothorax may occur in the apparently healthy, only in the past few years has much attention been paid to this fact. Hall,[1] in 1887, reported the first series of spontaneous pneumothorax in the healthy. Riesman and Fussel[2], in 1902, and Emerson[3], in 1903, were the first to report non-tuberculous pneumothorax in this country. Since these dates increasing numbers of cases in apparently normal people have been reported.

Many terms have been applied to this type of pneumothorax, including benign spontaneous pneumothorax, pneumothorax in the apparently healthy, and pneumothorax simplex. We prefer the term "idiopathic spontaneous pneumothorax," although it is not an entirely satisfactory designation.

The etiology of this form of pneumothorax is much debated. Kirshner[4] summarizes the most common theories as: (1) infectious, (2) congenital, and (3) emphysematous blebs on the surface of the pleura. He excludes the infectious theory because there is no pleural reaction (i.e. no subsequent effusion or empyema), and ordinarily no need for specific treatment (as in tension pneumothoraces complicating pulmonary infection). The relative frequency of the accident (spontaneous pneumothorax) as compared with the rarity of congenital defects argues against the second theory.

Rupture of subpleural blebs is the most practicable and widely accepted explanation of the etiology. Gordon[5] has described five cases in which he could delineate bullae on the roentgenogram after reexpansion had occurred. Kirshner[4] noted a ruptured pleural bleb at necropsy in one case of fatal termination and believed it to be an area of localized emphysema from collections of air under the pleura which can come only from the lungs. According to Kirshner, a rupture of an alveolus or a terminal bronchiole must occur, with the escape of air into the interstitial tissue and dissecting along the septum to cause a localized bleb on the

pleura. The constant gliding of the parietal over the visceral pleura in this area gradually thins the pleura over the bleb which may rupture on cough or mild exertion.

Kjaergaard[6], in 1932, reviewed the literature and found six cases in which the lesion had been "elucidated anatomically at autopsy." In these six cases, the pneumothorax was caused by rupture of the superficial air vesicles at the apices of otherwise healthy lungs. Three of these vesicles resulted from multiple congenital malformations of the lung, and in the other three, from solitary air vesicles on the bases of cicatricial changes.

The true incidence of idiopathic spontaneous pneumothorax is hard to determine because it may occur with little or no symptoms. Blackford[7] has found an approximate ratio of one case for every thousand students in session at the University of Virginia.

The symptoms, when present, are usually brought on by exertion. Coughing, sneezing, laughing, and straining at stool have been reported as precipitating factors. A third of Perry's[8] patients were seized with pain in the early morning. The symptoms vary ordinarily in direct proportion to the degree of collapse and the displacement of the trachea and mediastinal structures. The onset of pain may or may not be associated with dyspnea. In its location, the pain may simulate angina or coronary occulsion, with characteristic radiation to the neck and down an arm.

The diagnosis of pneumothorax may be suspected from the history and confirmed by physical findings and subsequent roentgen examinations. The radiographic exclusion of any parenchymal pathology as well as negative sputum examinations (if any is obtainable) are of primary importance in classifying the case as idiopathic. Our experience is in agreement with Friesdorf[9] and Olbrechts[10] in finding the average frequency of negative tuberculin tests as noted in other apparently healthy individuals. Likewise, the sedimentation rate of the erythrocytes usually is normal. The electrocardiogram may show an axis shift indicative of mediastinal cardiac rotation.

In simple idiopathic spontaneous pneumothorax, the prognosis is excellent. The condition may recur once or several times, but the patients survive with but few exceptions. Other than a week's rest in bed, no treatment is indicated with the rare exception of a tension pneumothorax which necessitates withdrawal of air. No after care is necessary because recurrences cannot be prevented by any known treatment.

Analysis of Cases

Over the past four year period, forty-nine cases of pneumothorax have been observed at the Cleveland Clinic. In ten of these patients a final diagnosis of idiopathic spontaneous pneumothorax was made. In the remaining thirty-nine cases, the pneumothorax was found to be a compli-

cation of the following diseases: silicosis, chronic pulmonary fibrosis with emphysema, asthma, lung abscess, pneumonia, atelectasia, tumors (both primary and metastatic), osteomyelitis of a rib, and tuberculosis. Tuberculosis was present in only ten cases.

Of the ten cases of idiopathic spontaneous pneumothorax, there were eight men and two women. The average age was twenty-eight years, the youngest patient being sixteen and the oldest, forty-three years of age.

Seven of the patients had experienced single attacks only. Of the other three, one had had two attacks, one, four, and the other, eight. The cases were evenly divided as to the side of predilection; four cases experienced right sided pneumothoraces, four, left sided, and one, bilateral.

The presenting symptoms in five cases so accurately simulated a coronary accident that a tentative diagnosis of this entity was made by the initial physician attending the case. In two cases the electrocardiogram revealed an axis shift compatible with mediastinal rotation with lung collapse (these two cases experienced extensive degrees of collapse). The tracings were entirely negative otherwise. The symptoms occurred during exertion in six of the ten cases: (1) A sixteen year old boy noted the onset of left chest pain with dyspnea while sprinting a 100-yard dash. (2) A twenty-six year old mechanic noted right sided symptoms while turning a wrench at work. (3) A forty-three year old mortician experienced right sided chest symptoms while carrying a casket. (4) A thirty year old salesman noted the onset of left chest pain while coughing. (5) A thirty-two year old man noted onset of right chest symptoms while running up stairs. (6) A thirty-six year old man, a window trimmer by occupation, noted the onset of his left chest symptoms immediately following a short fall from a ledge. He did not strike his chest and experienced no kind of fracture.

Case Reports

The following two cases illustrate (1) a typical single idiopathic spontaneous pneumothorax, and (2) a patient experiencing multiple bilateral attacks.

Case 1: A twenty year old college student experienced sudden pain in the right anterior chest while eating breakfast on July 28, 1939. He had been feeling perfectly well, had been symptom-free prior to the onset of the pain, and had had no kind of injury. The pain became progressively worse and was associated with dyspnea and some nausea. He was confined to bed for three or four days with a constant "pleurisy pain." Following that date, he felt quite well except for a recurrence of the original symptoms for a lesser duration while playing tennis, ten days prior to being seen at the Clinic on August 22, 1939. He had experienced no cough at any time, and his past and family history were noncontributory. There was no family or contact history of tuberculosis.

Examination of the chest revealed a decreased expansion of the right lung with a hypersonorous percussion note over the upper and outer right chest, and decreased breath sounds in the same area. No rales were heard. The tempera-

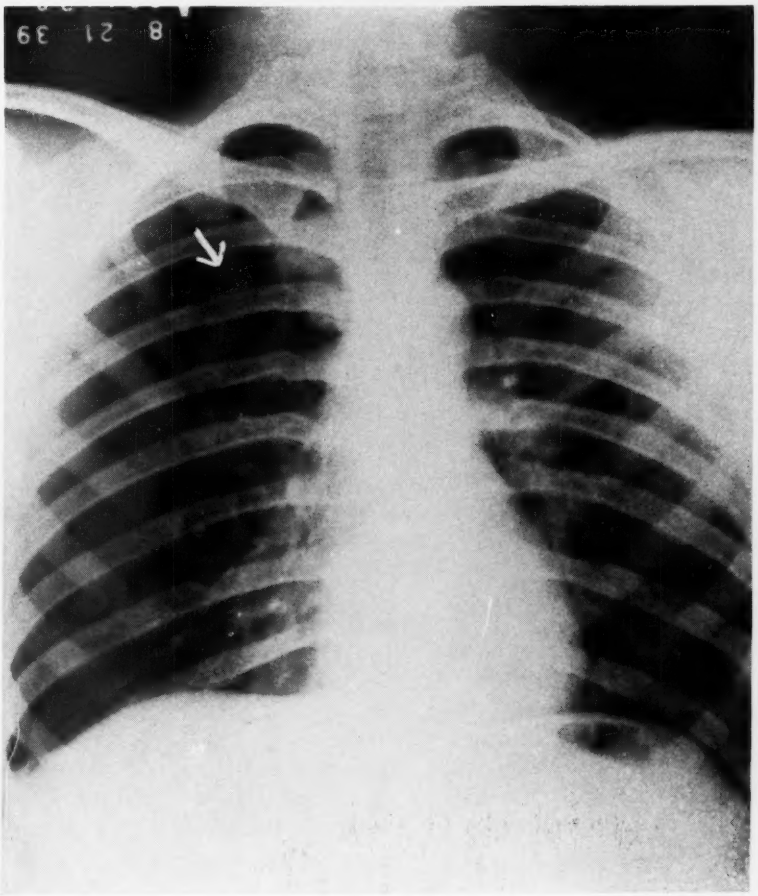


FIGURE 1: Roentgenogram showing 40 per cent collapse of the right lung. Arrow points to irregularity which might be interpreted as a ruptured pleural bleb.

ture and pulse rate were normal. The remainder of the examination was entirely negative. Tuberculin tests were negative in all strengths.

The roentgen examination (Fig. 1) revealed a 40 per cent collapse of the right lung. At one point on the apical lateral aspect of the visceral pleura of the collapsed lung was observed a small irregularity, which might be interpreted as a ruptured pleural bleb (note arrow). The lung parenchyma was entirely clear bilaterally.

A roentgenogram taken fifteen days later (Fig. 2) revealed complete reexpansion of the affected lung with no sign of any parenchymal infiltration. He has remained perfectly well to the present time.

Case 2: A forty-three year old mortician was first seen at the Clinic in

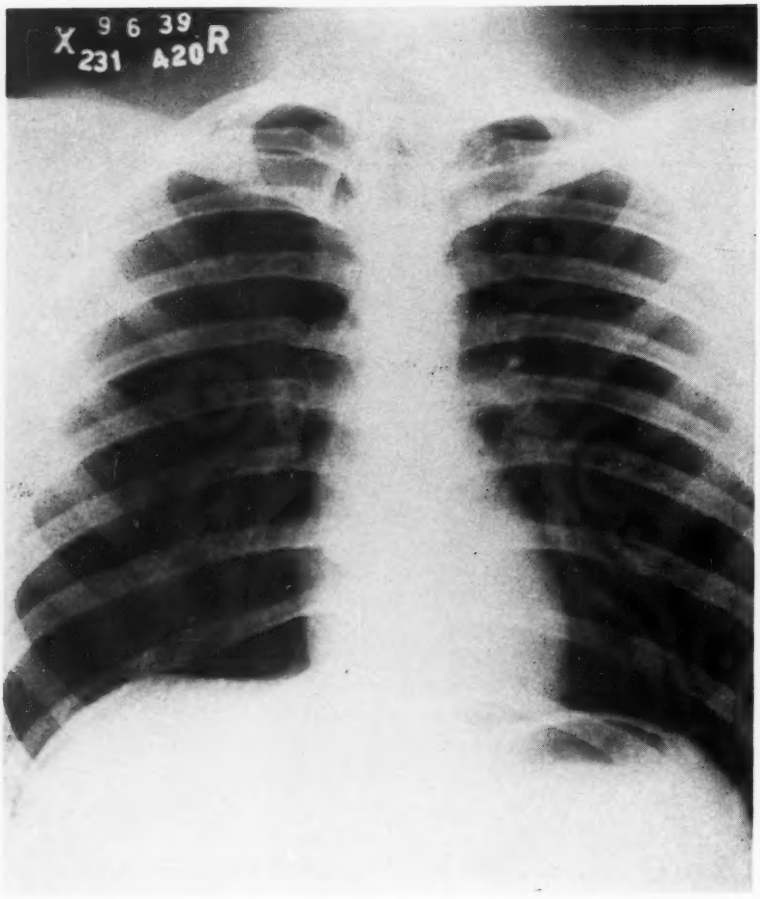


FIGURE 2: Roentgenogram taken fifteen days later showing complete reexpansion of the right lung and no parenchymal infiltration.

October, 1936. He dated the onset of dull mid-anterior chest pain with marked dyspnea to lifting a casket one week previously.

He had had a right chest pain with dyspnea while playing golf in 1923. At that time, a spontaneous pneumothorax was confirmed by roentgen examination, and he was confined to bed for six weeks. In 1928, during a short illness which was diagnosed as influenza, he again experienced a right spontaneous pneumothorax, and was confined to bed for six weeks.

In the intervals between the above attacks and prior to the attack which brought the patient to the Clinic, he apparently had enjoyed the best of health. He never had had a chronic cough or hemoptysis. He stated that three sputum specimens (examined at the time of colds and the influenza) had been negative. The family history was negative.

The physical examination, substantiated by roentgen studies, revealed evidence of bilateral pneumothorax. There was a complete collapse of the right lung, and a 30 per cent collapse of the left lung. No demonstrable parenchymal infiltration was present. The remainder of the examination and various other diagnostic and laboratory studies were negative. A sputum specimen was negative, and the sedimentation rate was normal.

The patient recovered satisfactorily from this attack and remained symptom-free until he experienced a recurrence on the right side in May, 1937, while walking up a hill. He recovered from this attack and apparently has remained free from attacks on restricted activities to the present. Since his initial visit, he has been seen at frequent intervals, and all examinations have failed to reveal any evidence of tuberculosis or other explanation for the repeated spontaneous pneumothoraces.

Summary

Idiopathic spontaneous pneumothorax apparently is unrelated to tuberculosis, and occurs in healthy individuals in whom there is no demonstrable evidence of tuberculosis. Series of cases reported in the literature would indicate that: (1) The incidence of negative tuberculin tests is proportionate to apparently healthy individuals not experiencing this pleural accident and (2) there is no higher incidence of subsequent development of tuberculosis than in the average non-tuberculous population.

At present there are three theories to explain the etiology of the condition: (1) Infectious (non-tuberculous), (2) congenital, and (3) rupture of emphysematous (subpleural) blebs. The latter is the most practicable and the most widely accepted theory and is discussed in detail.

The prognosis is excellent in simple idiopathic pneumothorax, with few exceptions. There is no indicated treatment other than a week's rest in bed with the rare exception of a case with tension pneumothorax which necessitates withdrawal of air. No after care is necessary because recurrences cannot be prevented by any known treatment.

A series of cases is reviewed, and two cases are reported in detail.

References

1. Hall, F. de H.: On cases of pneumothorax in persons apparently healthy, Tr. Clin. Soc. Lond., 20:153-161, 1886-7.
2. Fussel, M. H. and Riesman, D.: Spontaneous non-tuberculous pneumothorax, Am. J. M. Sc., 124:218-235, (August) 1902.
3. Emerson, C. P.: Pneumothorax; a histological, clinical, and experimental study, Johns Hopkins Hosp. Rep., Balt., 11:1-450, 1903.
4. Kirshner, J. J.: Spontaneous pneumothorax; aetiological considerations, Am. Rev. Tuberc., 40:477-481, (October) 1939.
5. Gordon, I.: Benign spontaneous pneumothorax, Lancet, 2:178-181, (July) 1936.
6. Kjaergaard, H.: Spontaneous pneumothorax in apparently healthy, Acta Med. Scandinav., supp. 43:1-159, 1-93, 1932.
7. Blackford, S. D.: Spontaneous pneumothorax in college students, J.A.M.A., 113:737-739, (August 26) 1939.
8. Perry, K. M. A.: Spontaneous pneumothorax, Quart. J. Med., 8:1-21, (January) 1939.
9. Friesdorf, C.: Ein Beitrag zur Aetiologie und Pathologenese des nichttuberkulösen Spontanpneumothorax, München med. Wshnschr., 74:1672-1674, (September) 1927.
10. Olbrechts, E.: Le pneumothorax spontane "idiopathique," Benin, Ann. de med., 27:429-483, (May) 1930.

CLINICAL APPLICATION OF SHORT WAVE DIATHERMY

W. J. ZEITER, M.D.

Medical diathermy is the production of heat in the body tissues for therapeutic purposes by high frequency currents, insufficient in amount, however, to produce temperatures high enough to destroy the tissues or to impair their vitality.

With the development of radio, powerful oscillator tubes have been constructed for the production of high frequency oscillations of shorter wave lengths. The usual 300 to 400 meter wave length of conventional diathermy is now 30 to 6 meters in short wave diathermy. To distinguish between these two methods the Council on Physical Therapy of the American Medical Association has given the term "conventional diathermy" to the older method and "short wave diathermy" to the newer method. At the present time it probably is better not to make a division of ultra-short wave diathermy since evidence that this subdivision is necessary still is lacking.

Short wave diathermy is rapidly replacing conventional diathermy. No doubt exists that the application of the new method is more simple and the danger of burns is markedly reduced. In short wave diathermy, the plates are not in direct contact with the skin, as is necessary in conventional diathermy. Short wave diathermy can produce a burn, but the danger is minimal if the proper technic is used.

Short wave diathermy is divided into two types; namely, (a) the electromagnetic field, and (b) the electric field. When the electromagnetic field is utilized, the current is conducted to the patient by means of a heavy, very flexible, insulated cable which is used as the electrode, and is coiled about or around the part to be treated. The electric field is applied by means of condenser pad electrodes or cuff electrodes which encircle the part to be treated, and the so-called air space electrodes made of metal contained in glass, bakelite, or rubber.

The condenser pad electrode consists of a flexible metal plate between two layers of flexible rubber which prevent the current from arcing from the metal to the patient's skin. Various machines have different sized electrodes. The cuff electrodes are similar to the condenser pad electrodes except for their size, which ranges from three to nine inches in width and from two to forty-eight inches in length. When applied to the body, they are placed so that they entirely encircle the part to be treated. The air space electrode is made of a circular disk which is adjusted within a special glass container or encased within hard or soft rubber. They are made so that the electrodes can be placed within any desired distance of the skin.

The usual and accepted length of time for a treatment with short

wave diathermy is from twenty to forty minutes. In conventional diathermy the milliamperage indicates the amount of current flowing. However, in short wave diathermy the dose or intensity of current is determined mainly by the patient's tolerance.

In treating a pathological condition with heat, it is important to visualize the process in the tissues and not to use diathermy to the exclusion of other methods of treatment. In many instances short wave diathermy is a valuable adjunct to other forms of therapy.

In the various types of arthritis, adequate treatment is essential. The various physical agents are important adjuncts to treatment, and physical agents alone should not be relied upon in the treatment of this disease. Rest is of prime importance in most instances. Foci of infection should be eliminated, anemia and lowered metabolism should be corrected, and if the patient is obese, weight reduction is important.

The patient with arthritis usually requires treatment over a long period of time and simple physical methods of treatment should be employed. Short wave diathermy is not a necessity, but if it is available, it should be used especially for treating the larger joints such as the shoulder, back, hips, and knees. The local application of heat increases circulation and tissue metabolism in the involved part, and a sedative effect also is obtained. In an acute rheumatic joint, the first application of short wave diathermy should be at low intensity and for a period of time shorter than the usual treatment. When there is congestion in a joint, added excess heat may increase the congestion and intensify the symptoms. Treatments can be given every day if the patient is in the hospital and every other day if the patient is an out-patient. In addition to local heat, the systemic application of heat is of value in increasing circulation and metabolism. This is especially true when many joints are involved and they cannot all be treated locally. If at home, the patient can apply heat daily from an infra-red generator or the paraffin bath which is especially suitable for the hands.

Massage must be given at frequent intervals, and should follow the application of heat. This also can be done at home by some interested member of the family who has received instruction in the procedure. Heavy massage over an arthritic joint may cause a marked local reaction. Therefore, the prescription for this should be made specific by the physician.

During the acute phase, rest in proper supports is important. Passive manipulation should be avoided because it may increase swelling and interfere with the circulation which already is poor. Sunbaths from the natural source should be taken whenever possible, and the ultra-violet lamp should be used in the winter.

Short wave diathermy aids in relieving the pain and muscle spasm in bursitis, and in promoting the absorption of the calcareous deposits.

Diathermy usually aggravates the symptoms in the very acute stage. The severe pain in acute subacromial bursitis makes bed rest almost essential. Abduction of the arm and a few pounds of traction will give immediate relief in most cases. The application of moist heat during the first few days is most beneficial. It may be followed by infra-red irradiation and later by low intensity short wave diathermy. If the symptoms are aggravated after the first treatment of from five to ten minutes at low intensity, infra-red baking should be used for a day or two. When treatment with short wave diathermy is tolerated, the daily treatment time may be increased until treatments can be given for twenty to twenty-five minutes.

In acute bursitis there often is considerable distention of the bursa, which causes very severe pain. Kendrick[1] suggests needling or needle irrigation of the bursa, especially if relief is not obtained by traction and moist heat. Massage should follow the use of heat in all cases and as full a range of motion as possible should be executed each day. This usually is not difficult, especially if the muscle spasm has been overcome by a short period of traction.

It is well known that calcareous deposits in chronic bursitis will disappear without treatment. If the deposits persist, however, diathermy should be tried before surgical intervention is undertaken. Massage and exercise are essential for restoring the joint to normal function. In the painful bursa with calcific deposits and marked limitation of motion, treatment with diathermy, massage, and exercise should be given daily until the symptoms are relieved. Then treatments can be given at longer intervals. In these patients the general treatment is as important as the local treatment. Eradication of foci of infection, regulation of diet, systemic heliotherapy or any measure to generally improve the physical condition should be utilized.

The use of short wave currents in the treatment of fractures has been justified by its effect upon the injured soft tissues. It has not been proved, however, that diathermy has any specific action beyond that of centrally producing heat in the tissues and bone. Massage and exercise should be used in conjunction with heat.

Although diathermy has been suggested for delayed or nonunion of fractures, few reports have appeared in the literature to support this suggestion. Voshell[2], who reported thirty-eight cases of delayed union of fractures, still considered his investigation to be in the preliminary stages. Some of his earlier patients had been treated with conventional diathermy, the more recent ones with short wave diathermy. In this group, thirty fractures showed clinical union, three improved, and nonunion occurred in seven. He states, "Definite thickening of the soft callous surrounding the fracture occurs after eight or more treatments and this steadily hardens and thickens until union occurs; in conjunction

with this the hinge-like abnormal mobility slowly diminishes." The beneficial effect probably is due to the hyperemia produced by the heating effect.

Osborne and Coulter[3] have demonstrated that the bone marrow temperature of dogs can be elevated with short wave diathermy in the living animal, and that the temperature of the muscular tissue can be elevated to a greater degree than that of the bone marrow. The thermal gradient from the surface to the interior of the limb eliminates the danger of any damage to the bony structure. More clinical and experimental data must be available before any definite conclusions can be drawn as to the value of short wave diathermy in the treatment of fractures and the nonunion of fractures.

Whenever a sprain or dislocation occurs, muscles, blood vessels, ligaments, tendons, and the synovial membrane are injured. Hemorrhage and swelling is produced with muscle spasm. There is an inflammatory reaction with heightened local metabolism and elevation of the temperature. For the physiologic effect, local application of cold with rest, proper compression bandaging, and elevation are indicated for immediate treatment. After the first day or two, local edema, lessened circulation, and decreased local metabolism necessitate applications of local heat. If the affected joint is immobilized with a removable plaster cast or splint, the cast may be removed so that heat may be applied locally. It is well to begin with daily infra-red baking for fifteen to twenty minutes, followed by massage. After the danger of hemorrhage has passed, diathermy should be applied to increase local circulation and to reduce pain and swelling.

In acute myositis, the application of the infra-red lamp or hot fomentations, in addition to rest and light massage, have been more effective than has diathermy. However, short wave diathermy is indicated when the condition becomes chronic and presents the picture of a fibrositis with the formation of nodes or areas of induration. In addition, heavy massage and exercise should be utilized.

In a review of fibrositis, Krusen[4] states that almost every writer on this subject considers the judicious application of heat followed by a special type of deep local massage to be almost specific.

In the last few years, with the introduction of specific serums and sulfanilamide and its derivatives, the treatment of pneumonia has undergone a change. Diathermy is not considered a specific cure for pneumonia, nor is there sufficient critical evidence that it lowers mortality or changes the course of the disease. However, it is a helpful adjunct because it is the best method for the application of deep heat for reducing the severity of thoracic pain. This symptomatic relief is often important.

Schmitt[5] states, "Adequate dosage is determined by the intensity of current, duration of each treatment, and frequency of treatments, which

will safely establish and maintain an effective active hyperemia. In all patients treated, the relief from dyspnea, cyanosis, and pain was marked; it takes place during and after the first treatment, and is usually quite complete after a second treatment. The fact that these patients are without distress in any position in the prone posture is the best evidence of such relief."

In reviewing the results obtained with short wave diathermy, Brugsch and Pratt[6] found a high percentage of cures in lung abscess. They treated two acute cases and six chronic cases in which they were unable to obtain similar results. Whether or not short wave diathermy will cure acute lung abscesses is still not definitely established clinically.

For acute enteritis and severe irritable colon, heat in its various forms has been found to be very effective. Short wave diathermy, used as an adjunct to medical treatment, is very valuable for the rapid relief of spasm and for its sedative effect also.

Occasionally a case of severe vesical spasm is seen following electroresection of the prostate. Although we have too small a number of patients to report, we have used short wave diathermy in ten and have observed the disappearance of spasm in all the patients. In vesical spasm and irritable colon, treatments are given twice daily.

Ruedemann and I[7] have studied sixty patients who were treated with short wave diathermy for ocular conditions.

The chief factor in all acute diseases of the eye is to administer immediate treatment to the affected part. The eye does not tolerate infection or inflammation very well. Recovery is usually very poor and the visual loss may be great. We believe that deep diathermy offers a medium for immediate treatment. Short wave diathermy, both as heat therapy and for lessening the amount of deep orbital pain, is of definite benefit in those patients who have acute inflammatory glaucoma. It has a definite beneficial effect in cases of orbital and ocular inflammation, especially the acute cases, in deep corneal ulcers, and in the early stages of central venous thrombosis.

Short wave diathermy is an excellent adjunct to treatment and should be tried in many more cases until the proper field for this form of therapy is found. It surpasses superficial heat in all lesions of the orbit. Very few patients complain of any discomfort and the vast majority are improved by the therapy.

Since it is possible to heat the bony structures with short wave diathermy, various reports have appeared as to its value in the management of nasal sinusitis. Short wave diathermy was evaluated by Hollender[8] in two series of patients in both the acute and chronic form, with controls. Local deep heating in the region of the sinuses produces analgesia through hyperemia and hyperlymphia, improves tissue metabolism, increases resorption and consequently brings about a more rapid defensive

response to infection. In acute sinusitis, short wave diathermy in itself is not sufficiently effective as a therapeutic agent and may occasionally lead to serious consequences unless it is used as a therapeutic aid to other procedures. This agent was valueless in the large majority of cases of chronic disease of the maxillary sinus. Our experience has been that expressed by Hollender, in that short wave diathermy is used as an adjunct to accepted therapeutic measures.

In neuritis and neuralgia, an accurate diagnosis should be made and, if possible, the etiological factors should be eliminated. General medical measures should be employed and short wave diathermy advocated. The response varies and in some instances the patient is made worse rather than relieved. In other instances, complete and sudden relief may be obtained. Therefore, short wave diathermy should be given a therapeutic test to determine its effectiveness. In the acute stage, treatments at low intensity should be used first to determine the effect and to gauge subsequent treatments.

Short wave diathermy has been especially valuable in the treatment of Bell's palsy. More recently it has been substituted for infra-red baking in the early stages of this disease. Here again it is used at low intensity and for short duration. When applying it by the electromagnetic induction method, a soothing, deep heat is obtained which increases the circulation and reduces inflammation in the involved area. As soon as the pain has disappeared, stimulation with the galvanic current should be used on the affected muscles. The patient should be given instructions for exercises, and support with adhesive tape should be applied to prevent sagging of the face and stretching of the muscles.

Contraindications to this form of therapy are as follows:[9]

"It is important to keep the contraindications for diathermy in mind. The local application of high frequency currents is contraindicated in the case of certain acute inflammatory processes such as acute nondraining cellulitis and acute infectious arthritis, or any condition in which there is a tendency to hemorrhage, such as a gastric ulcer; over areas in which the appreciation of heat has been impaired or lost, as in the case of certain peripheral nerve injuries; through the abdomen, pelvis or lower part of the back during pregnancy; during menstruation or thirty-six hours before or after menstruation, and over areas where a malignant growth is suspected."

Summary

It is believed that the indications for the use of short wave diathermy are essentially the same as those for the use of conventional diathermy.

The ease of application and the lessened danger of burns are the chief advantages.

Short wave diathermy should be used as an adjunct in the treatment of

disease when it is so indicated. It has a very definite place in the treatment of disease and with its effective heating, it may be of greater use than conventional diathermy, or its use may produce successful clinical results where conventional diathermy has failed.

Further research and careful evaluation of clinical results are necessary.

References

1. Kendrick, J. I.: Physical therapy principles of periarthritis of the shoulder, Arch. Phys. Therapy, 21:41-44, (January) 1940.
2. Voshell, A. F.: Delayed union of fractures; analysis of cases, Arch. Phys. Therapy, 18:561-564, (September) 1937.
3. Osborne, S. L. and Coulter, J. S.: Thermal effects of short wave diathermy on bone and muscle, Arch. Phys. Therapy, 19, 281-284, (May) 1938.
4. Krusen, F. H.: Physical therapy of fibrositis, Arch. Phys. Therapy, 18:687-697, (November) 1937.
5. Schmitt, Milton G.: Treatment of pneumonia by electromagnetic induction; preliminary report, Arch. Phys. Therapy, 17:299-304, (May) 1936.
6. Brugsch, H. G. and Pratt, J. H.: Short wave diathermy in treatment of lung abscess, J.A.M.A., 112:2114-2119, (May) 1939.
7. Ruedemann, A. D. and Zeiter, W. J.: The use of diathermy in ophthalmology, (Publication pending).
8. Hollender, A. R.: Short wave diathermy in treatment of nasal sinusitis, Arch. Otolaryng., 30:749-754, (November) 1939.
9. Council on Physical Therapy: Medical Diathermy, J.A.M.A., 112:2047, (May 20) 1939.

STUDIES ON BLOOD WATER

C. P. WOFFORD, M.D., E. PERRY MCCULLAGH, M.D. and
D. ROY MCCULLAGH, Ph.D.

In an attempt to determine more accurately the degree of dehydration of patients with definite fluid imbalance, particularly patients with Addison's disease, an effort was made to find a rapid and simplified method of determining the total blood water. The method finally selected embodies the fundamental principles of many procedures described since the original work in 1845.

Venous blood was collected from the arm in routine fashion and 5 cc. were placed immediately into 8 cc. tightly stoppered glass flasks containing 0.1 cc. of a 20 per cent solution of potassium oxalate as the anticoagulant. Glass Petri dishes were layered with one-eighth to one-quarter inch of clean white sand and heated for four hours at a temperature between 96 and 102° C. These were allowed to return to room temperature in a desiccator. The sand was used to afford a larger surface area for the blood film, and to prevent any possible spattering.

The first series of fifty-nine determinations differed from the later work in only two respects: (1) 2 cc. volumetric pipettes were used, and (2) the Petri dish with sand was not weighed until after the addition of the blood sample. Obviously, this eliminated the possibility of expressing the results in this group in terms of per cent by weight. In the second group of determinations, eighty-four in all, Folin 2 cc. volumetric pipettes were used, after being recalibrated. All weights and volumes used in calculating the results are the corrected weights and volumes.

In all but the first group, the previously dried Petri dish with sand was weighed to an accuracy of 1 mg. Two cc. of blood were delivered into each dish and the second weighing was made. The dish was then placed in an electric oven for from four to five hours at a temperature of 96 to 102° C. This time interval was purely an arbitrary one. When comparative determinations were made, however, after keeping duplicate samples in the oven for as long as twenty-four hours, no appreciable difference in the results was obtained. After the drying process, the Petri dish was placed in a desiccator and allowed to return to room temperature before the final weighing was made.

The weight of the blood water in the sample was determined directly by the difference between the readings before and after heating. The percentage of blood water was calculated by dividing the weight of the water by the weight of the blood sample. A final calculation was made by dividing the weight of the blood water by the volume of the blood sample in order to express the results in terms of grams of water per 100 cc. of blood.

TABLE 1

NORMAL VALUES FOR TOTAL BLOOD WATER, EXPRESSED IN PER CENT

Author	*Range Per Cent*	*Sex*
Becquerel and Rodier	76 — 80	males
Becquerel and Rodier	77.3 — 81.3	females
Arronet	78.03 average	
Biernacki	77.3 average	
Schwendter	77.2 — 81.5	
Schneider	80.11 average	
C. Schmidt	78.9 — average	males
C. Schmidt	82.4 — average	females
Stintzing and Gumprecht	76.9 — 80.4	males
Stintzing and Gumprecht	78.5 — 81.6	females
Kuroda	76.14 — 81.34	males
Kuroda	77.50 — 83.56	females
Kuroda, et al	72.5 — 87	
Diaz, Bielschowsky and Minon	78.25 — 81.47	
Brown and Roth	79 — 83	
Wofford, McCullagh and McCullagh	78.24 — 81.32	

RESULTS

A small series of twelve normal individuals was used for this study. Their blood water contents varied from 78.24 per cent to 81.32 per cent, or, when expressed in terms of grams of water per 100 cc. of blood, they varied from 82.81 to 85.37 per cent. The corresponding hematocrit figures were 47 to 39 cc. of packed cells. Table 1 shows that our normal values compare favorably with some of those found in the literature. The determinations of total blood water showed a standard devia-

tion of 2.46 ± .19 and a coefficient of variation of 3.08 ± .24 when the blood water was recorded in per cent by weight; and a standard deviation of 1.86 ± .11 and a coefficient of variation of 2.18 ± .13 when recorded in grams per 100 cc.

In the entire series, a linear relationship was observed between the hematocrit and the blood water. The trend (k) in the first group was − .276 and in the second, − .24. This relationship showed that the total blood water and the hematocrit were almost mirror images of each other. It would seem, therefore, that the hematocrit yields almost as much information about the percentage water content of the blood as does actual blood water determination and, since it entails less time and effort, it is the procedure of choice.

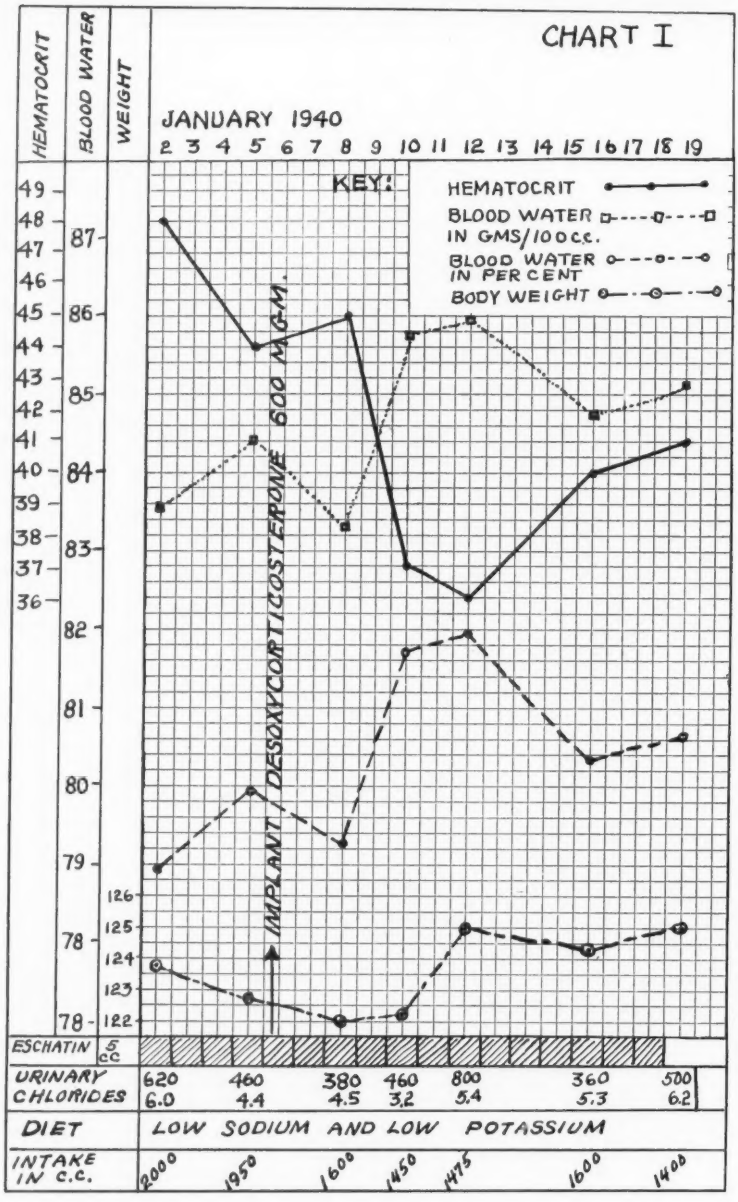
From the line of regression and the coefficient of variation, an equation was derived for calculating the blood water from any given hematocrit reading, with the theoretical error the same as the calculated error in this series of experiments. The equation is as follows:

$$y = 80 - (45 - x)\,k$$

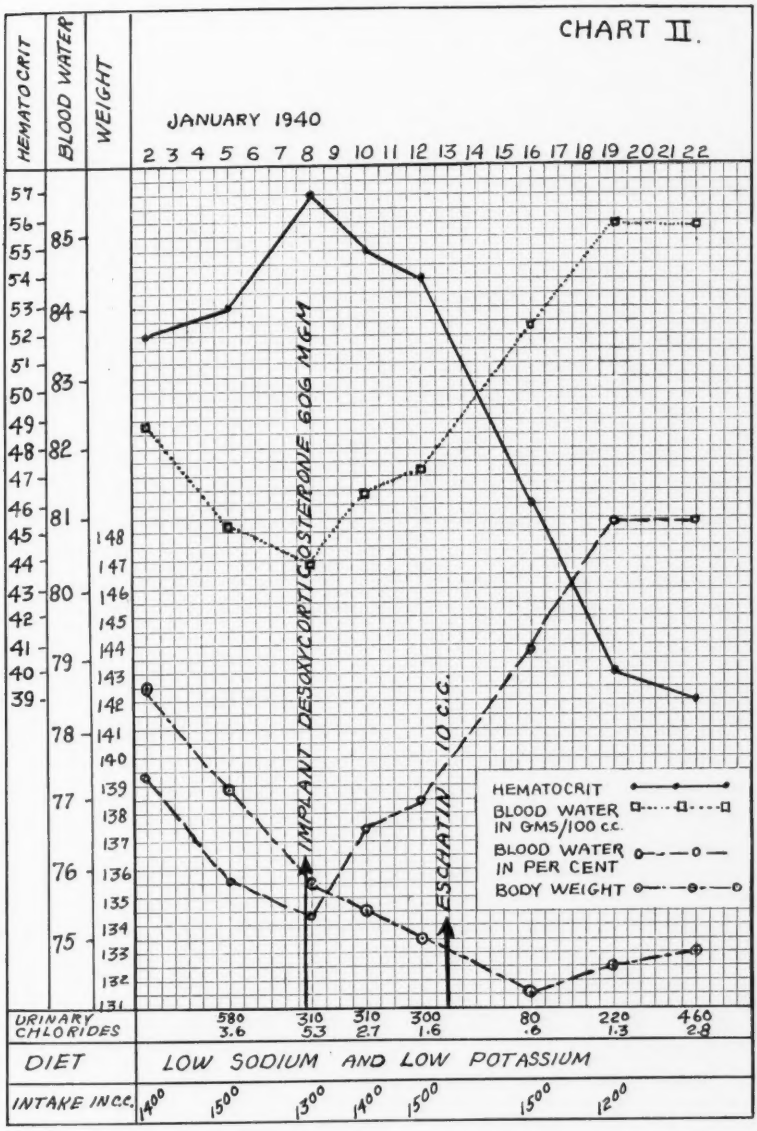
y = blood water in per cent by weight
x = hematocrit reading in cc. of packed cells
k = trend

Six cases of Addison's disease were studied in detail. Even though it is assumed that relatively little shift occurs in the quantity of water circulating in the blood in normal individuals, tremendous variations were found in three of the six cases of Addison's disease. In the first two patients, the changes were observed following implantation of 600 mg. of desoxy-corticosterone (Charts I and II), and in the third, the change was observed as the patient recovered from an acute addisonian crisis. Her blood water content increased from 78.17 per cent to 85.38 per cent within three days. In one other patient who received an implant of desoxy-corticosterone, there was no abrupt shift in hemoconcentration. The first two patients were on low sodium and low potassium diets throughout the period of these studies. Although specimens of food were not analyzed daily, the diet was accurately weighed and an attempt was made to keep constant the intake of sodium and potassium. Their sodium intake approximated 2 gm. per day and the potassium intake varied from 1.4 to 1.6 gm. per day. In the third patient, the intake of sodium chloride decreased from 37 to 20 gm. per day, while the daily intake of potassium ranged from 1.0 to 1.6 gm. The last patient received a low potassium diet containing about 1.6 gm. of potassium daily, but with no additional sodium chloride.

The weight changes were not significant. In one of the cases, there was a steady loss of weight which continued for eight days after the blood water content began to increase. In this patient, the urinary chlorides reached a minimum when the weight curve was at its lowest point. In the other patients, there was a corresponding reflection of the urinary



URINARY CHLORIDES ARE STATED AS MG. PER 100 C.C. AND AS TOTAL EXCRETION PER DAY IN GRAMS



URINARY CHLORIDES ARE STATED AS MG. PER 100 c.c. AND AS TOTAL EXCRETION PER DAY IN GRAMS

chlorides and changes in body weight. No relationship was noted, however, between body weight and blood water.

From the miscellaneous cases studied here, some interesting observations were made. Those patients with polycythemia vera showed no striking deviations from normal. One case with a severe hypochromic anemia had an increased blood water percentage which was in keeping with the decreased hematocrit reading. Other patients with hypochromic anemia did not show this variation. One patient with massive hemorrhage from a peptic ulcer revealed a marked increase in the water content of the blood with a corresponding decrease in hematocrit levels. When considered in groups of disease entities, these patients did not reveal any constant similarities in their blood water contents.

Summary

1. A simple method for determining the water content of the blood is described.

2. The results are expressed both as per cent by weight and as grams per 100 cc.

3. In this series, the normals compared closely with those of other workers.

4. The blood and hematocrit readings bore an inverse relationship which could be expressed mathematically.

5. No correlation could be made between the water content of the blood and the volume index, color index, total red cell count, hemoglobin, or blood volume.

6. Considerable shifts in the blood water content were found in individual patients from day to day.

7. An equation was derived from which the water content of the blood could be calculated from any given hematocrit reading.

The authors wish to express their appreciation to Mrs. M. I. Sparks and to Dr. D. P. Quiring for their assistance in these studies.

OVARIAN HORMONE THERAPY IN FUNCTIONAL MENOMETRORRHAGIA

Preliminary Report

E. J. RYAN, M.D.

This brief preliminary report is presented at the present time because of the gratifying results obtained from the use of cyclic estradiol benzoate and progesterone therapy in ten cases of functional menometrorrhagia. Clinical investigation is still in progress, and a more detailed record will be submitted subsequently. This method of therapy has been effective in certain stubborn cases where other methods have failed.

Browne[1] has reported the successful treatment of metropathia hemorrhagica with premenstrual progesterone following curettage. The endometria of those cases which we have treated have not shown the changes found in metropathia hemorrhagica. It has been our impression from previous experience that cyclic use of the sex sterols has proved more effective in our cases. This is still to be verified.

Our application of estrone, or estradiol benzoate, and progesterone therapy has been limited to those cases of menorrhagia and/or metrorrhagia which are "functional" in character as determined by careful history, examination, assays and endometrial biopsies. Indirectly responsible organic disease and endocrine aberrations, such as hypothyroidism, must be excluded first.

Our original conception of the cyclic use of sex sterols in the treatment of functional menometrorrhagia developed as a consequence of finding low urinary assays for estrogenic substances in such a case early in 1938. This has been confirmed by assays in other cases, and has been correlated with endometrial biopsies. We felt that the condition was due to hypo-ovarianism and that the logical treatment would be an attempt to reproduce in the endometrium those changes which would occur there normally. Various commercial estrogens and progesterone preparations are highly potent, and have been shown to be capable of producing normal premenstrual endometria in human castrates[2].

Since that time, Hamblen[3, 4] has advanced an interesting theory in support of the use of estrogens and progesterone in menometrorrhagia, and has reported a series of cases treated successfully by both the oral and the intramuscular routes. He feels that refractivity on the part of either the ovary or the endometrium, or both, may be a primary factor in many cases of functional menometrorrhagia. Under such circumstances he reasons, it is logical to employ the hormones of the ovary cyclically since this therapy, by its retrograde action on the pituitary, might be effective in overcoming ovarian refractivity. Moreover, the

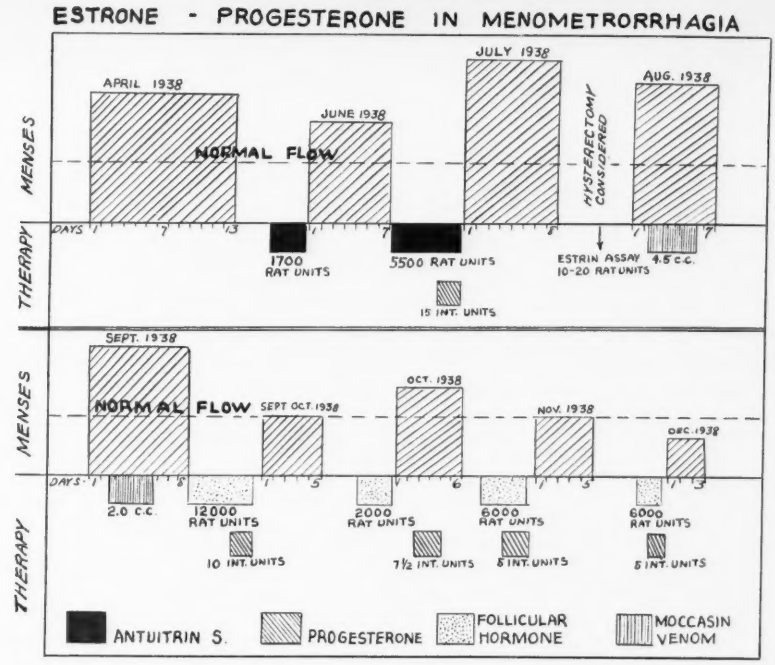
stimulating action of these products on the endometrium might favorably influence its refractivity.

Our use of estrone, or estradiol benzoate and progesterone, has been designed to produce the desired effect with the minimal quantity of the hormonal preparations necessary for good results. On the basis of our studies, the following mode of therapy should prove effective in many instances, and may be modified in the direction of greater or lesser dosage as required by the individual case. It has been effective when large doses of APL have failed.

Treatment may be initiated at any time, even during an episode of metrorrhagia, since estrogen injections usually are sufficient to stop hemorrhage. Injections are then given on the basis of a twenty-eight day cycle, 2,000 rat units of estradiol benzoate, or 10,000 international units of estrone, being given two or three times weekly during the first three weeks. During the fourth week, two to five international units of progesterone are given on the fifth and third days before the onset of the calculated menstrual period. Therapy is then withheld for three or four days, after which the course is initiated again without regard for the presence or absence of bleeding, and is repeated on the above-mentioned twenty-eight day basis. Estrogen sometimes may be given with the two injections of progesterone, but it is likely to delay the onset of bleeding. When a fairly definite cycle is present or has been established it usually has been our custom to give the estrogen and progesterone only during the two weeks preceding menstruation in total divided dosage of 4,000 to 8,000 rat units of estradiol benzoate and two to ten international units of progesterone. With this method, estradiol benzoate and progesterone probably should be given concurrently during the fourth week on the fifth and third days premenstrually. After four to six months of such cyclic usage, therapy should be withheld for a time to determine whether or not a normal rhythm and flow have been reestablished.

We do not recommend this method of treatment to the exclusion of other more commonly employed procedures. Pregnancy urine and placental preparations, testicular hormone, pregnant mare's serum derivatives, and even roentgen therapy and surgery have certain applications. Moccasin snake venom is sometimes an emergency measure. Curettage is helpful from the diagnostic standpoint and may be effective in controlling hemorrhage. It is preferable to do a curettage before beginning therapy with hormones, especially in women over thirty years of age, where malignancy has to be considered more seriously than in younger women. Thyroid may be used empirically with benefit in many cases, and may be especially helpful if the metabolism is low.

Our dosage has been considerably less than that employed by Hamblen[3] and the progesterone particularly has been far below the



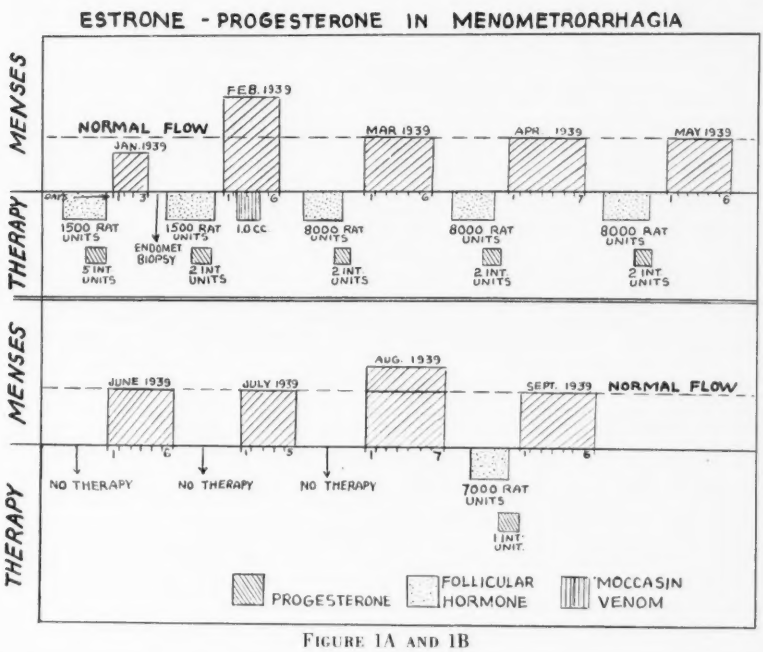


FIGURE 1A AND 1B

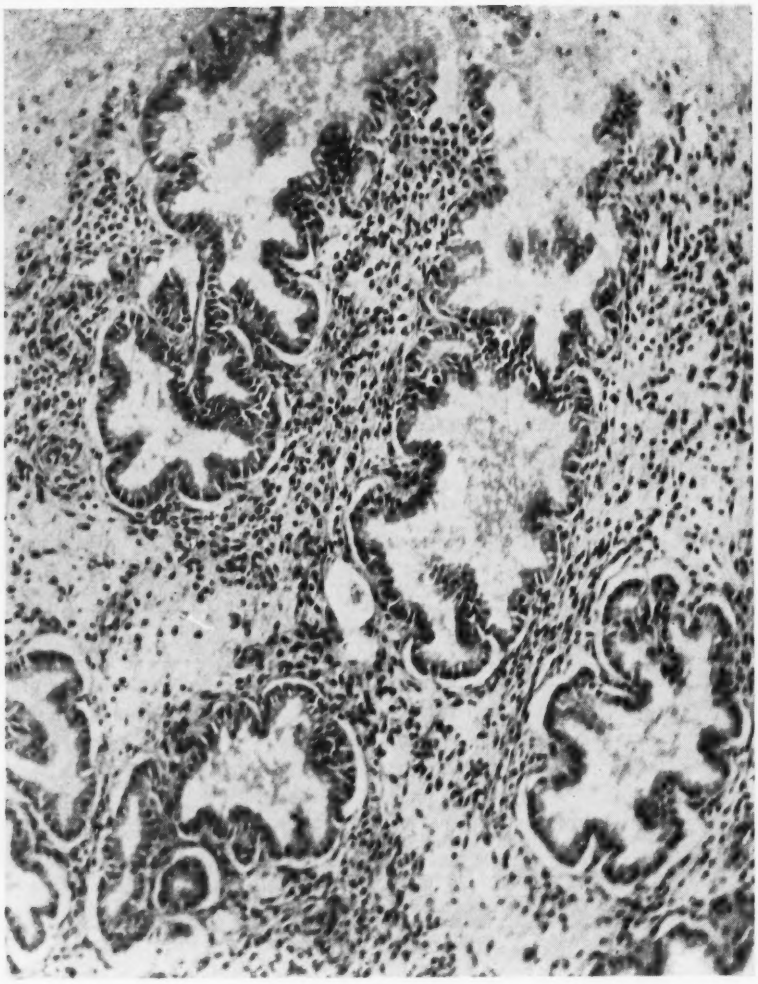


FIGURE 2: Endometrial section, Date: March 29, 1938.

minimal requirements for castrates, as outlined by Kaufmann[2]. Nonetheless, in approximately twelve cases, our results have been distinctly favorable, with but two exceptions. The following case is fairly typical:

CASE REPORT

A twenty-seven year old woman was seen originally in March, 1938, relative to her menorrhagia. This was the first case in which we employed cyclic follicular and luteal hormonal therapy. The idea originated with the finding of a low assay for estrogenic substances in the urine, indicative of hypo-ovarianism. The patient

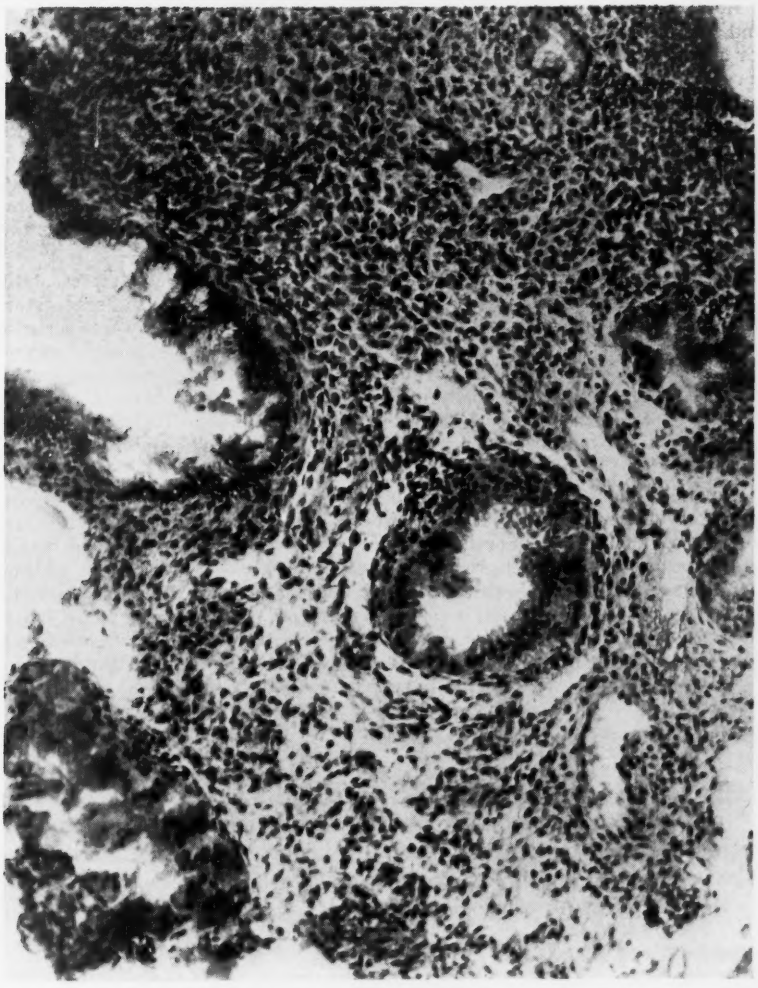


FIGURE 3: Endometrial section, Date: January 17, 1939.

had had regular but excessive and prolonged bleeding for a number of years. Large doses of antuitrin-S in February, 1935, and of APL in October, 1935, had proved ineffective. Removal of an ovarian cyst in July, 1936, was followed by a decrease in the duration of periods to eight or nine days, but the flow continued to be excessive. She had no unusual premenstrual symptoms but there was a rather profuse leukorrhea, which was exaggerated before and after the menstrual flow.

General physical examination revealed normal findings. The pelvic examination was negative.

Routine laboratory investigation, including urinalysis, blood counts, serology, and determination of the blood sugar level showed no significant findings, except for a hypochromic anemia which has been treated by iron medication. An assay for estrogenic substances was distinctly low, showing less than ten rat units in a twenty-four hour specimen of urine collected at approximately the midcycle. A subsequent assay showed ten to twenty rat units. The method used for these assays is that described by McCullagh and Guillet[5].

An endometrial biopsy two days before the onset of the menstrual period showed marked thickening with enlarged tortuous glands, lined by cuboidal and columnar epithelial cells, with infoldings into the lumina. There was marked edema and diffuse hemorrhage into the stroma.

The following charts represent her response to treatment over a representative period. (Figs. 1a and 1b). To a great extent, these charts are self-explanatory. It will be noted that antuitrin-S was not effective. Hysterectomy was seriously considered at one point. Completely normal bleeding was ultimately attained by the use of 8,000 rat units of estradiol benzoate and two international units of progesterone, employed cyclically in the manner described. Several months of normal flow resulted without therapy. The only untoward symptoms noted as a consequence of treatment were a sensation of pelvic fullness and mild cramping pain.

Figures 2 and 3 are photomicrographs of endometria collected on the day preceding or on the first day of bleeding, representing the findings before treatment and those following five months of therapy. There is relatively little difference in the two and each shows progesterone effect. This is in accordance with our opinion and that of others that such functional bleeding may occur from almost any type of endometrium, and is very common from that showing a mixed follicular and luteal hormone response. Bleeding from a purely proliferative endometrium, in our experience, has been somewhat less common than anticipated.

The fact that there is so little difference in the two specimens suggests that some factor[3] other than endometrial change, as a result of treatment, is responsible for the good results which were obtained.

Summary

A method of treatment for functional menometrorrhagia with cyclic estrogens and progesterone is presented. A typical case is discussed. The results are satisfactory, and the method is tentatively recommended. Further confirmatory investigation is in progress.

References

1. Browne, J. S. L.: (abstract) Some effects of sex hormones on certain abnormalities of corpus luteum function, Canad. M. A. J., 39:84-85, (July) 1938.
2. Kaufmann, C.: Umwandlung der Uterusschleimhaut einer kastrierten Frau aus dem atropischen Stadium in das sekretorischen Funktion durch Ovarialhormone, Zentralbl. f. Gynäk, 56:2058-2061, (August) 1932.
3. Hamblen, E. C.: Therapeutic use of the sex sterols in functional meno-metrorrhagia, Endocrinology, 24:13-28, (January) 1939.
4. Hamblen, E. C., Powell, N. B., Cuyler, W. Kenneth, and Pattee, C. J.: Oral use of pregneninonol in functional menometrorrhagia, Endocrinology, 26:201-207, (February) 1940.
5. McCullagh, D. R. and Guillet, R.: Summary of some laboratory methods in endocrinology, Cleveland Clin. Quart., 6:95-104, (April) 1939.

ADIE'S SYNDROME

Report of Four Cases

W. JAMES GARDNER, M.D. and F. L. SHIVELY, JR., M.D.

Adie's syndrome is characterized by two features: a tonic pupil and absent tendon reflexes. This condition has been recognized by neurologists for many years, but there has never been an adequate explanation of the etiology and pathogenesis. In 1902, Saenger[1] and Strasburger[2] simultaneously described the condition. Since this description, the syndrome has been given various names, such as the tonic pupillary reaction, pupillotonia, myotonic convergence reaction, and tonic convergence of pupils apparently inactive to light. In 1931 Adie[3] gave an adequate and concise description of the condition. From a study of twenty-two cases, he found that these cases seemed to fall into two definite groups: (1) The complete form with a typical tonic pupil and absence of tendon reflexes, and (2) the incomplete forms which he further subdivided into (a) the tonic pupil alone, (b) atypical phases of the tonic pupil alone ("iridoplegia," "internal ophthalmoplegia"), (c) atypical phases of the tonic pupil with absent reflexes, and (d) absent reflexes alone.

In Adie's syndrome the dilatation of the pupil is unilateral and it does not respond to light when the usual methods are used for eliciting the light reflex. After the patient has been placed in a darkened room for a long period of time, the pupils become equal in size. If a bright light is flashed into the affected pupil following this procedure, it responds slowly. As soon as the light is removed, the pupil returns to its original size. The most important feature of the tonic pupil is that it responds to convergence and accommodation only after prolonged effort. The pupil is never miotic and responds to mydriatics and miotics.

Because of the apparent loss of the light reflex with or without loss of the tendon reflexes, these patients are frequently thought to be suffering from syphilis of the central nervous system. Frequently, the tonic pupil has been erroneously called an "Argyll-Robertson pupil," "atypical Robertson pupil," etc. This is not good practice because (1) the pupil does not correspond to the postulates of Argyll-Robertson and (2) the use of such terms implies that the patient has syphilis. Adie has gone so far as to say, "The true Argyll-Robertson sign is an infallible sign of syphilis." The Argyll-Robertson pupil, as described by its original author, is small, usually bilateral, constant in size, and unaltered by light or darkness. It contracts promptly on convergence and dilates promptly when the effort to converge is relaxed. It dilates slowly and imperfectly to mydriatics. Thus it differs in every respect from the tonic pupil (Table 1).

Routine laboratory investigation, including urinalysis, blood counts, serology, and determination of the blood sugar level showed no significant findings, except for a hypochromic anemia which has been treated by iron medication. An assay for estrogenic substances was distinctly low, showing less than ten rat units in a twenty-four hour specimen of urine collected at approximately the midcycle. A subsequent assay showed ten to twenty rat units. The method used for these assays is that described by McCullagh and Guillet[5].

An endometrial biopsy two days before the onset of the menstrual period showed marked thickening with enlarged tortuous glands, lined by cuboidal and columnar epithelial cells, with infoldings into the lumina. There was marked edema and diffuse hemorrhage into the stroma.

The following charts represent her response to treatment over a representative period. (Figs. 1a and 1b). To a great extent, these charts are self-explanatory. It will be noted that antuitrin-S was not effective. Hysterectomy was seriously considered at one point. Completely normal bleeding was ultimately attained by the use of 8,000 rat units of estradiol benzoate and two international units of progesterone, employed cyclically in the manner described. Several months of normal flow resulted without therapy. The only untoward symptoms noted as a consequence of treatment were a sensation of pelvic fullness and mild cramping pain.

Figures 2 and 3 are photomicrographs of endometria collected on the day preceding or on the first day of bleeding, representing the findings before treatment and those following five months of therapy. There is relatively little difference in the two and each shows progesterone effect. This is in accordance with our opinion and that of others that such functional bleeding may occur from almost any type of endometrium, and is very common from that showing a mixed follicular and luteal hormone response. Bleeding from a purely proliferative endometrium, in our experience, has been somewhat less common than anticipated.

The fact that there is so little difference in the two specimens suggests that some factor[3] other than endometrial change, as a result of treatment, is responsible for the good results which were obtained.

Summary

A method of treatment for functional menometrorrhagia with cyclic estrogens and progesterone is presented. A typical case is discussed. The results are satisfactory, and the method is tentatively recommended. Further confirmatory investigation is in progress.

References

1. Browne, J. S. L.: (abstract) Some effects of sex hormones on certain abnormalities of corpus luteum function, Canad. M. A. J., 39:84-85, (July) 1938.
2. Kaufmann, C.: Umwandlung der Uterusschleimhaut einer kastrierten Frau aus dem atropischen Stadium in das sekretorischen Funktion durch Ovarialhormone, Zentralbl. f. Gynäk, 56:2058-2061, (August) 1932.
3. Hamblen, E. C.: Therapeutic use of the sex sterols in functional meno-metrorrhagia, Endocrinology, 24:13-28, (January) 1939.
4. Hamblen, E. C., Powell, N. B., Cuyler, W. Kenneth, and Pattee, C. J.: Oral use of pregneninonol in functional menometrorrhagia, Endocrinology, 26:201-207, (February) 1940.
5. McCullagh, D. R. and Guillet, R.: Summary of some laboratory methods in endocrinology, Cleveland Clin. Quart., 6:95-104, (April) 1939.

ADIE'S SYNDROME

Report of Four Cases

W. JAMES GARDNER, M.D. and F. L. SHIVELY, JR., M.D.

Adie's syndrome is characterized by two features: a tonic pupil and absent tendon reflexes. This condition has been recognized by neurologists for many years, but there has never been an adequate explanation of the etiology and pathogenesis. In 1902, Saenger[1] and Strasburger[2] simultaneously described the condition. Since this description, the syndrome has been given various names, such as the tonic pupillary reaction, pupillotonia, myotonic convergence reaction, and tonic convergence of pupils apparently inactive to light. In 1931 Adie[3] gave an adequate and concise description of the condition. From a study of twenty-two cases, he found that these cases seemed to fall into two definite groups: (1) The complete form with a typical tonic pupil and absence of tendon reflexes, and (2) the incomplete forms which he further subdivided into (a) the tonic pupil alone, (b) atypical phases of the tonic pupil alone ("iridoplegia," "internal ophthalmoplegia"), (c) atypical phases of the tonic pupil with absent reflexes, and (d) absent reflexes alone.

In Adie's syndrome the dilatation of the pupil is unilateral and it does not respond to light when the usual methods are used for eliciting the light reflex. After the patient has been placed in a darkened room for a long period of time, the pupils become equal in size. If a bright light is flashed into the affected pupil following this procedure, it responds slowly. As soon as the light is removed, the pupil returns to its original size. The most important feature of the tonic pupil is that it responds to convergence and accommodation only after prolonged effort. The pupil is never miotic and responds to mydriatics and miotics.

Because of the apparent loss of the light reflex with or without loss of the tendon reflexes, these patients are frequently thought to be suffering from syphilis of the central nervous system. Frequently, the tonic pupil has been erroneously called an "Argyll-Robertson pupil," "atypical Robertson pupil," etc. This is not good practice because (1) the pupil does not correspond to the postulates of Argyll-Robertson and (2) the use of such terms implies that the patient has syphilis. Adie has gone so far as to say, "The true Argyll-Robertson sign is an infallible sign of syphilis." The Argyll-Robertson pupil, as described by its original author, is small, usually bilateral, constant in size, and unaltered by light or darkness. It contracts promptly on convergence and dilates promptly when the effort to converge is relaxed. It dilates slowly and imperfectly to mydriatics. Thus it differs in every respect from the tonic pupil (Table 1).

TABLE 1

COMPARISON OF THE ARGYLL-ROBERTSON PUPIL AND THE TONIC PUPIL

Features	*Argyll-Robertson Pupil*	*Tonic Pupil*
Pupils		
1. Size of abnormal pupil	Small 75 per cent	Large 95 per cent
2. Abnormal pupil unilateral	5 per cent	90 per cent
3. Constant in size	Yes	No
4. Response to light	No contraction	Contraction only after prolonged stimulation
5. Response to darkness	No dilatation	Abnormal pupil may equal size of opposite pupil
6. Response on convergence	Immediate contraction	Very sluggish contraction
7. Response following convergence	Immediate dilatation	Reaction variable
8. Response of mydriatics	No dilatation	Immediate dilatation
9. Response to miotics	Slow contraction	Immediate contraction
10. Wassermann reaction	Positive	Negative

Adie, in 1932[4], published a second paper in which he reviewed forty-four reported cases, in nine of which there were absent tendon reflexes. Most of the patients had been examined by ophthalmologists, with little or no mention of the reflexes. When the reflexes were absent, they more than likely were regarded as further evidence of syphilis of the central nervous system. In Adie's own series, the tendon reflexes were absent in 68 per cent, or thirteen of nineteen cases. Loss of the Achilles reflex is the most common finding. Adie states that with both Achilles reflexes present he has never seen loss of any other jerks.

Case Reports

Case 1: A forty year old white woman came to the Clinic complaining of headache. She was very emotional and was upset easily. She complained of being chronically tired, becoming irritated very easily, and weeping upon the least provocation. Her husband was a chronic alcoholic.

Physical examination revealed the blood pressure to be 140 mm. systolic and 85 mm. diastolic. The right pupil was irregular and larger than the left. It did not react to light, but there was some reaction when it was subjected to prolonged convergence. The biceps, triceps, abdominal and patellar reflexes were diminished. The Achilles reflex was absent bilaterally. The Babinski reaction was negative. No sensory or motor changes were present.

Laboratory examination showed that the blood counts and the blood chemistry were within normal limits. Roentgenograms of the skull were normal. A spinal fluid examination exhibited normal dynamics. Wassermann and colloidal gold tests of the spinal fluid were negative and Wassermann and Kahn tests of the blood gave negative reactions. Urinalysis revealed nothing of significance.

Based upon these findings, a diagnosis of the complete form of Adie's syndrome was made.

Case 2: A sixteen year old white girl came to the Clinic with the complaint of "aching eyes" which had been present for four months. Approximately nine months prior to her admission to the Clinic she noticed that her right pupil was enlarged. She sought the advice of an ophthalmologist who refracted her eyes. The pupils were contracted for a few weeks after refraction, but the right pupil then returned to its original size. The remainder of the history was noncontributory.

Neurological examination revealed no objective evidence of an organic lesion of the central nervous system. The tendon reflexes were normal. There was no evidence of involvement of the third, fourth, or sixth cranial nerves. Ophthalmologic examination revealed the right pupil to be larger than the left and to be fixed to light. Examination of the visual fields showed a relative central field loss in the right eye which gave rise to the opinion that perhaps the patient had a retrobulbar lesion. Examination of the retina of the right eye showed a spot of old chorioretinitis just below the nerve head. Further examination revealed that the right pupil responded to the postulates set forth by Adie. With these findings, a diagnosis of the incomplete form of Adie's syndrome was made.

Case 3: A nineteen year old white girl came to the Clinic complaining of headache and blurring of vision. The headache was located just above the left eye and had been present for five months. It was continuous in nature and occasionally radiated to the parietal area. Occasional attacks of nausea and vomiting had been associated with the headache. The vomiting was described as

being projectile in character. About one month prior to admission to the Clinic, blurring of vision occurred. She also complained of photophobia. An ovarian dysfunction was present but this was not deemed pertinent to the present illness.

On physical examination the patient had a normal temperature, the pulse rate was 92 and the blood pressure 120 mm. systolic and 78 mm. diastolic. The pupils were irregular. The left pupil was dilated and did not react to light or accommodation upon the first examination. The right pupil was normal in all respects. Examination in the Department of Ophthalmology showed the left pupil to have no direct or consensual reaction to light. However, the pupil did contract after three minutes of fixed accommodation. Only a slight increase was noted in the size of the left pupil after the patient had been placed in a dark room for thirty minutes. At the end of this time, the pupils were equal in size. The left pupil reacted sluggishly to light after prolonged stimulation. Both pupils contracted promptly following the instillation of two drops of eserine.

The biceps, triceps, abdominal, patellar, and plantar reflexes on the left side were markedly diminished. The Achilles reflex on the left was absent. There were no pathological reflexes. No sensory or motor changes could be elicited.

Laboratory tests showed the blood counts and the blood chemistry to be normal. Urinalysis was negative in all respects. The Wassermann and Kahn tests of the blood gave negative reactions. Roentgenograms of the skull were reported negative for any intracranial pathology.

With these findings, a diagnosis of the complete type of Adie's syndrome was made.

Case 4: A twelve year old white girl came to the Clinic complaining of unequal pupils which had been present for a period of one year. The patient was the second child. She had been delivered without any obstetrical difficulty, and had developed normally in every respect. At the time of examination there were no complaints referable to the vision. The patient did have an occasional frontal headache but it was not believed to have any relation to the pupillary asymmetry. No nervous manifestations could be elicited. The family history was entirely negative and the remainder of the history was nonessential.

Physical examination showed a pulse rate of 78 beats per minute and a blood pressure of 100 mm. systolic and 60 mm. diastolic. The only significant findings pertained to the eyes and the tendon reflexes. The right pupil measured 6 mm. in diameter. It was round and, when stimulated by light, the direct and consensual response was absent. When the pupil was subjected to a strong light over a prolonged period of time there was only a slight contraction. The pupil responded to accommodation and convergence after prolonged effort. The left pupil measured 4 mm. in diameter and was normal in all respects. The visual fields were normal. There were no pathological changes in the fundi. The patient was then placed in the dark room for a period of thirty minutes but no change was noted in the size of the pupils. When the right pupil was stimulated by homatropine and eserine, it responded immediately. Examination of the tendon reflexes showed the biceps and patellars to be diminished. The Achilles reflexes were absent. There were no pathological reflexes and no sensory or motor changes.

The blood counts and the blood chemistry were within normal limits. Wassermann and Kahn tests of the blood gave negative reactions. The urinalysis was normal.

With these findings, a diagnosis of the complete form of Adie's syndrome was made.

Discussion

Although many theories have been advanced, the etiology and pathogenesis of Adie's syndrome still remains obscure. Many times the condition is asymptomatic. Moore[5] quotes a case of a patient who had been aware of the pupillary asymmetry for a period of forty-seven years, the condition being entirely asymptomatic. Kennedy[6] and his associates noted the frequency of emotional disturbances and vasomotor lability in their group of cases. Inman[7] also noted the relationship between emotional instability and the tonic pupil. Adie, however, stated that the nervous factor played no part in the etiology. The explanation for the loss of the tendon reflexes upon an unstable autonomic nervous system remains a problem of much conjecture.

As far as can be determined, Adie's syndrome is not congenital or hereditary. However, cases have been reported in which the patients have stated that the pupils have *always* been unequal. Adie states, "My impression is that the abnormal pupillary reaction may appear at any age." Women predominate over men. In Adie's own series (nineteen cases), women comprised 79 per cent of the cases. In his review of the literature (forty-four cases), 70 per cent of the cases were women. All four of our cases occurred in the female sex.

In a few instances, the onset appears suddenly with blurring of vision and upon examination a tonic pupil is found with or without absence of the tendon reflexes. The general health of these patients is remarkably good. In our series, we believe Case 1 has a very definite "nervous factor" which, according to Kennedy and others, accounts for the presence of the syndrome. However, in the other three cases, no factors of emotional instability were exhibited.

Adie believes that the reaction is an expression of a unique kind of perversion of pupillomotor activity. He states, "the curious manner in which stimuli are stored in excess and slowly emitted points to some change in the activity of the cells in the vegetative portion of the oculomotor nucleus. We are driven to the viscera for analogous types of innervation." He further states that the associated absence of tendon reflexes does not alter this opinion.

The treatment of Adie's syndrome, providing all other neurological diseases have been eliminated, is reassuring the patient. Particular attention should be given to patients in whom a previous diagnosis of syphilis has been made. An attempt should be made to control any emotional instability in the patient.

Conclusions

We have not attempted to explain the etiology or pathogenesis of this condition. This small group of cases recently has come to our attention and consequently has stimulated our thinking along this line.

Every possibility must be considered in an attempt to reach a diagnosis. Then, by exclusion, the patient may be placed into this category. Further study and more careful examination may reveal this syndrome to be more prevalent than it appears at present.

The actions and reactions of the tonic pupil have been discussed, particularly with reference to the Argyll-Robertson pupil with which it is so easily confused. In the table which is included, an attempt has been made to show the differences between the two totally different pupillary reactions.

The age of onset cannot be determined and the cause is unknown. There are no sequellae. The syndrome predominates in women.

Finally, we want to stress the fact that Adie's syndrome is a symptom-complex which superficially simulates tabes dorsalis, and is not due to syphilis.

References

1. Saenger, A.: Ueber myotonishe Pupillenbewegung, Neurolog. Centrabl., 21:837, 1902.
2. Strasburger, J.: Pupillentrögheit bei accommodation und convergence, Neurolog. Centrabl., 21:738, 1902.
3. Adie, W. J.: Pseudo-Argyll-Robertson pupils with absent tendon reflexes; Benign disorder simulating tabes dorsalis, Brit. M. J., 1:928-930, (May 30) 1931.
4. Adie, W. J.: Tonic pupils and absent tendon reflexes: Benign disorder sui generis; its complete and incomplete forms, Brain, 55:98-113, (March) 1932.
5. Moore, R. F.: Non-luetic Argyll-Robertson pupil, Brit. M. J., 2:843-844, (November 7) 1925.
6. Kennedy, F., Wortis, H., Reichard, J. D. and Fair, B. B.: Adie's syndrome: Report of Cases, Arch. Ophth., 19:68-80, (January) 1938.
7. Inman, W. S.: Non-luetic Argyll-Robertson pupil, Brit. M. J., 2:1179-1180, (December 19) 1925.

ESOPHAGEAL HIATUS HERNIA ASSOCIATED WITH HYPOCHROMIC ANEMIA AND ANGINA PECTORIS

Report of a Case

A. CARLTON ERNSTENE, M.D. and FRANK J. MCGURL, M.D.

The association of esophageal hiatus hernia with severe hypochromic anemia has been reported by a number of observers[1, 2, 3, 4, 5, 6]. The anemia is due to loss of blood from the gastro-intestinal tract, probably the result of congestion or erosion of the gastric mucosa proximal to the constricting ring of the hernia. In the case reported by Schiro and Benjamin[6], however, gastroscopic examination revealed no erosions and no differences in the mucosa above and below the diaphragm, although some of the gastric rugae were abnormally red. A review of fifty-nine cases of esophageal hiatus hernia at the Cleveland Clinic revealed two with hypochromic anemia. Since no examinations of the stool were made in one case, one cannot be certain that the anemia in this case was secondary to bleeding from the gastro-intestinal tract. The other case is the subject of this report.

REPORT OF CASE

A white married woman, sixty years of age, was admitted to the hospital on April 30, 1939, because of dyspnea on the least activity, palpitation, weakness and fatigability, and attacks of pain in the chest. Twelve years earlier, she had fallen down a basement stairway and had been unconscious for a period somewhat less than an hour. There had been no fracture. Dyspnea on exertion had been noticed for the first time after this accident and had become gradually but progressively worse. At the time of admission to the hospital, even the act of getting into or out of bed caused severe shortness of breath and palpitation. During the four months prior to admission, the patient had experienced attacks of pressure-like pain in the mid-substernal region with radiation to the right and left anterior chest and upward into the neck. These attacks were brought on only by exertion and were relieved within a few minutes by rest. Weakness and fatigability had been complained of for several years and had increased in severity for six weeks. A slight, unproductive cough had been present for six weeks, and for one week there had been some edema of the feet and ankles.

Physical examination revealed a moderately overweight individual with marked pallor of the skin and mucous membranes. The tongue was normal. "Spoon nails" were present. The lungs were clear on percussion and auscultation. The area of relative cardiac dullness extended 13 cm. from the midsternal line in the fifth intercostal space. The heart rhythm was regular, and the rate, 80 beats per minute. A moderate systolic murmur was heard in the third left intercostal space. The arterial blood pressure was 148 mm. systolic and 90 mm. diastolic. The liver edge could be felt just below the costal margin and was somewhat tender. There was slight pitting edema of the ankles.

The red blood cell count was 2,840,000 per cu. mm. and the hemoglobin content 28 per cent (4.4 gm. per 100 cc.). The color index of the erythrocytes was 0.49, the volume index 0.70, and the saturation index 0.70. The white blood cell count 4,400 per cu. mm. Examination of stained blood films showed severe pallor of the erythrocytes and marked anisocytosis and poikilocytosis. There were 2.5

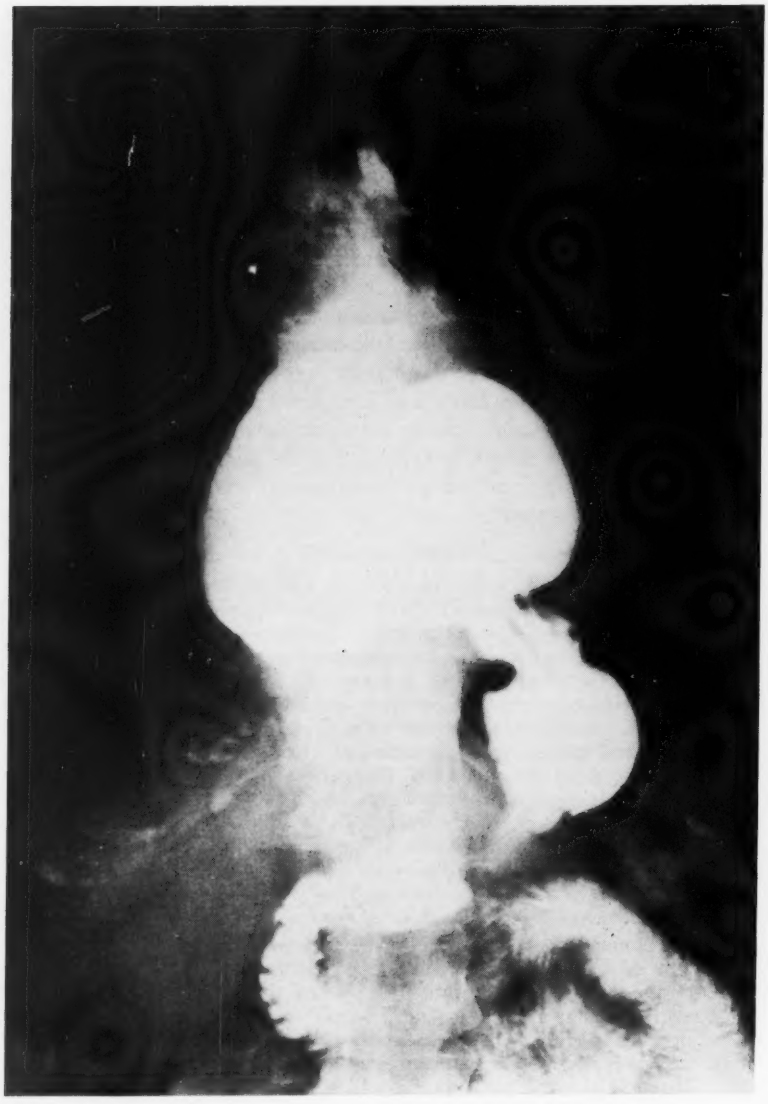


FIGURE 1: Roentgenogram showing a large esophageal hiatus hernia.

per cent reticulocytes. The icterus index was 3. The Wassermann and Kahn tests of the blood gave negative reactions. Urinalysis gave normal findings. Examinations of the stools showed from one plus to four plus occult blood.

Roentgenograms of the chest revealed that approximately four-fifths of the

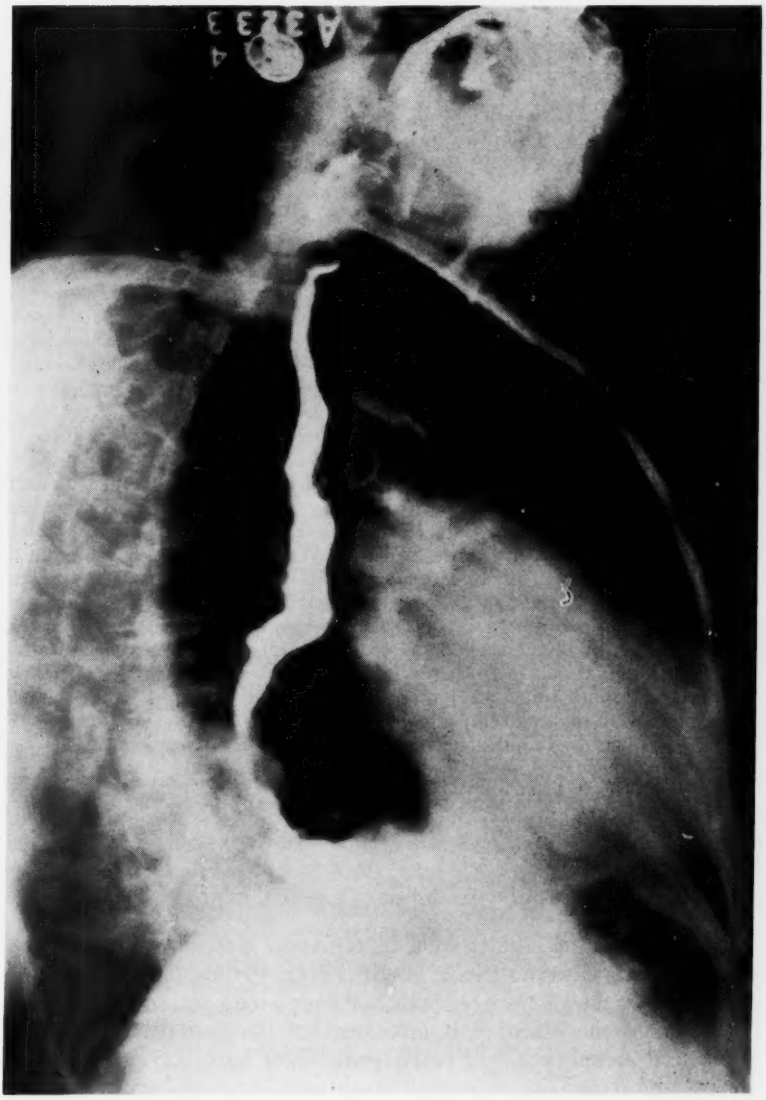


FIGURE 2: Roentgenogram showing esophagus of normal length.

stomach was in the thorax. The heart was enlarged. Further roentgenographic studies, after the administration of barium mixture, confirmed the presence of a large esophageal hiatus hernia (Fig. 1). The stomach was normal otherwise. The esophagus was of normal length (Fig. 2). The duodenum and the colon were normal except for a few small diverticula in the sigmoid region. The gall

bladder was visualized after the administration of cholecystographic dye and contained no stones. An examination of the gastric contents one hour after the administration of an Ewald meal showed a free acid content of 20 and a total acidity of 30.

An electrocardiogram revealed sinus rhythm with a rate of 84 per minute. Except for left axis deviation and slight depression of the S-T intervals in Lead I, the tracing was within normal limits in all respects. A precordial tracing (Lead IV F) was normal.

The following diagnosis was made: (1) Esophageal hiatus hernia, (2) arteriosclerotic heart disease with enlargement of the heart and angina pectoris, and (3) hypochromic microcytic anemia.

The patient remained in the hospital for nineteen days. Four transfusions of 500 cc. of whole blood were given, and Blaud pills were administered by mouth in doses of 30 grains (2 gm.) three times a day. In addition, thiamin chloride, 10 mgm., and liver extract, at first 3 cc. and later 1 cc., were administered daily by intramuscular injection. Seventeen days after admission to the hospital, the red blood cell count was 5,080,000 per cu. mm. and the hemoglobin content 78 per cent (12 gm. per 100 cc.). The color index of the erythrocytes was 0.76, the volume index 0.89, and the saturation index 0.86. With the correction of the anemia, there was striking symptomatic improvement. Weakness and fatigability diminished rapidly and a general sense of well-being replaced the earlier malaise. Dyspnea no longer occurred when the patient walked at an ordinary gait, and there were no further attacks of substernal pain. At the time of discharge from the hospital, the patient was advised to follow a high vitamin, low carbohydrate diet with extra vitamins. Blaud pills were continued for ten weeks in doses of twenty grains (1.3 gm.) three times a day. The clinical course has been entirely uneventful and the patient has been able to carry out all ordinary activities without dyspnea or anginal pain. On a few occasions, however, excessive exertion has caused mild dyspnea which has been relieved promptly by rest. The roentgenographic studies of the stomach were repeated on May 27, 1940, and the size of the hernia was found to be unchanged. An electrocardiogram taken on the same day also was unchanged, and the stools contained no occult blood.

The course of the erythrocyte count and hemoglobin content of the blood are shown in Table 1. Because of the slightly reduced values recorded in May, 1940, the administration of Blaud pills was resumed and will be continued periodically from now on.

Discussion

The presence of occult blood in the stool indicates that the severe anemia in this case must have resulted from the loss of small amounts of blood from the gastro-intestinal tract over a long period of time. The exact site of the bleeding is unknown but the fact that anemia is a recognized complication of esophageal hiatus hernia makes its gastric origin almost certain. Congestion or erosion of the gastric mucosa, therefore, would seem to be the most probable cause of the hemorrhage. The incidental presence of diverticula in the sigmoid introduces some uncertainty, but diverticula seldom are responsible for blood loss sufficient to cause severe anemia.

The relief of the patient's symptoms with the correction of the anemia makes it evident that neither the dyspnea nor the attacks of substernal

pain were due directly to the presence of a large part of the stomach in the thorax. Esophageal hiatus hernia occasionally gives rise in a purely mechanical way to symptoms which are highly suggestive of angina pectoris[7,8], but in such cases a careful analysis of the symptoms usually enables one to differentiate the pain from that of angina pectoris. In the present case, the pain met all of the requirements for a diagnosis of angina pectoris, and the clinical course indicated that the attacks were

TABLE 1

EFFECT OF TREATMENT ON THE ERYTHROCYTE COUNT AND HEMOGLOBIN CONTENT OF THE BLOOD

Date	*Red Blood Cells*	*Hemoglobin*
	millions	*per cent*
5/1/39	2.84	28
5/9/39	4.00	41
5/12/39	4.46	65
5/18/39	5.08	78
6/20/39	5.19	81
8/22/39	4.83	81
11/20/39	4.73	84
5/27/40	4.36	78

due primarily to the presence of severe anemia in an individual who probably has only slight coronary artery disease. The role of anemia in producing angina pectoris in patients who have but little coronary artery disease is well known.

SUMMARY

A case in which a patient with a large esophageal hiatus hernia experienced attacks of angina pectoris and dyspnea on slight activity has been reported. Severe hypochromic anemia due to loss of blood from the gastro-intestinal tract also was present, and correction of the anemia resulted in relief of the patient's symptoms.

REFERENCES

1. Segal, H. L.: Secondary anemia associated with diaphragmatic hernia, New York State J. Med., 31:692-695, (June) 1931.
2. Weitzen, M.: Diaphragmatic hernia with severe anemia, Am. J. Roentgenol., 28:808-812, (December) 1932.
3. Bock, A. V., Dulin, J. W. and Brooke, P. A.: Diaphragmatic hernia and secondary anemia; 10 cases, New England J. Med., 209:615-625, (September) 1933.
4. Eisen, D.: Oesophageal hiatus hernia (with special reference to its x-ray diagnosis), Canad. M. A. J., 39:207-213, (September) 1938.
5. Corn, A., Calton, R. and Claisse, R.: Grave anemia with hernia of stomach in adult case, Bull. et Mem. Soc. Med. d hop. de Paris, 55:1130-1135, (July) 1939.
6. Schiro, H. S. and Benjamin, J. E.: Severe anemia associated with diaphragmatic hernia, Ohio State M. J., 36:164-166, (February) 1940.
7. Ernstene, A. C.: Differential diagnosis of coronary artery disease, J. Kansas M. Soc., 36:441-446, (November) 1935.
8. Jones, C. M.: Tr. Am. Clin. and Clim. Assoc., 55:1939 (In Press).

LICHEN NITIDUS

A Report of Two Cases, with an Unusual Finding of Melanin in Giant and Epithelioid Cells in One Case

GEO. H. CURTIS, M.D.

Lichen nitidus was first described in 1907 by Pinkus[1] who reported nine cases, all men. The principal clinical characteristics of the disease are small discrete papules no larger than a pinhead, having a flat surface, being round or vaguely polygonal shaped, bright pink in color, and distributed on the penis, chest, and arms. In 1909 Arndt[2] reported twelve cases, all with lesions on the penis, and in one case, on the buccal membrane also. Kyrle and McDonagh[3] reported a case in England in 1909, Sutton[4] reported a case in the United States in 1910, and Civatte[5] reported the first case in France in 1911.

Including the two cases in this report, I have been able to find reports of only ninety-five cases of lichen nitidus in the English, French, and German literature. The disease is uncommon, but because of the lack of symptoms which otherwise would announce its presence, it is probably more common than supposed.

In a review of the literature, Niles[6] presented three theories for the etiology of lichen nitidus: (1) Tuberculous, because of a clinical and histologic association between tuberculosis and lichen nitidus in some cases, (2) a variety of lichen planus because, in other cases, there is a clinical and histologic resemblance between the two, and (3) in still other cases, lichen nitidus has the independent clinical and histologic picture of an inflammatory granuloma of unknown cause.

The evidence for tuberculous etiology includes: positive tuberculin reactions and an accentuation of the lesions (one case)[7]; the presence of tuberculosis elsewhere in the body and on the skin; the finding on microscopic examination of acid-fast granules in the lesions of lichen nitidus (one case); a certain histologic similarity between cutaneous tuberculous lesions and lichen nitidus; and finally, the disappearance of the lesions under tuberculin therapy (one case)[8]. As evidence against a tuberculous etiology, all animal inoculations have given negative results; the lesions may be present for years without change; the penis (an area almost always free from other forms of cutaneous tuberculosis) is a site of predilection; caseation or necrosis in the lesions, as is usually seen in tuberculosis cutis, never occurs; and the disease often occurs in individuals who present no evidence of tuberculosis.

Barber[9], Dowling[10], Haynes and Hellier[11], Ellis and Hill[12], and others believe that lichen nitidus may be a variation of lichen planus. In the cases studied by them, lesions of lichen planus and lichen nitidus were coexisting, and it was impossible to determine whether some of the

lesions were lichen nitidus papules or lichen planus papules. Furthermore, some lesions varied histologically between typical lesions of each disease. In other cases, an attack of lichen planus followed shortly after the disappearance of a lichen nitidus eruption.

The consensus of most dermatologists is that lichen nitidus is an independent entity of unknown cause. The several diseases from which lichen nitidus must be differentiated, namely, lichen scrofulosorum, lichen planus, and verruca plana juvenilis in typical form, on careful examination, bear little or no resemblance to lichen nitidus in clinical or histologic characteristics. In the absence of a known cause for lichen nitidus, its relation to tuberculosis and lichen planus cannot be confirmed.

At first glance, lichen nitidus clinically resembles lichen planus to a moderate degree. The lesions usually are of pinhead size or smaller and have a glistening surface. They are sharply defined, circular or polygonal in outline, slightly raised above the level of the skin, pinkish in color, or of the same hue as the surrounding skin. Usually the papules have no relation to hair follicles, but by careful search, a papule surrounding a hair follicle is found occasionally[13, 14]. Upon close examination, some of the papules are seen to be umbilicated, and usually occur in groups without coalescence of individual papules. The favorite sites for the lesions are the genitalia, the abdomen, breast, flexor surfaces of the elbows, wrists, and palms. The lesions or groups of lesions may be generalized and have been observed in the mouth, on the neck and on the soles. Barber[14] described patches in generalized cases as being pityriasiform or psoriasiform, and reddish yellow, brownish yellow, or reddish violet in color. Subjective symptoms usually are absent, but there may be slight itching. The disease is chronic, although it may disappear spontaneously.

Because of an unusual finding of pigment in the microscopic examination of lesions in one case, and because in both cases the eruption disappeared within a few months under superficial roentgen therapy, the following cases are reported.

Report of Cases

Case 1: A negro, twenty-five years of age, came to the Clinic on February 20, 1940, complaining of an eruption on the penis, trunk, and extremities which he first noticed three months previously. At times, the lesions itched slightly. Before his mother's death from pulmonary tuberculosis in 1926, he had been in close association with her. Since then, he had had a number of examinations for tuberculosis at the city health clinics, but no evidence of tuberculosis was found.

General physical examination showed a well developed, well nourished young negro of sthenic habitus without abnormalities. A roentgenogram of the chest showed no evidence of tuberculosis.

The striking feature of the eruption was the numerous discrete papules, all of

the same size and somewhat smaller than a pinhead, evenly and thickly distributed on the skin of the penis (Fig. 1). The papules were sharply defined, roughly

FIGURE 1: Case 1. Lichen nitidus.

circular, elevated slightly above the skin surface, and of a paler hue than the normal skin color. Their surfaces were flat and glistening, and some showed tiny central depressions. Careful examination of the eruption on the rest of the body showed the papules to be interfollicular. On the neck, trunk, and extremities, the papules were aggregated into irregularly shaped groups of as few as twelve papules up to more than a hundred. The groups were irregularly distributed on the neck, shoulders, chest, back, abdomen, arms, about the elbows, forearms, dorsa of the hands, thighs, and legs. At the elbows the grouping was triangular in shape with the vertex toward the wrists. The face, scalp, buccal mucous membrane, fingers, palms, and soles showed no lesions.

The hemogram and urinalysis were normal. The fasting blood sugar level was 85 mg. per 100 cc. and Wassermann and Kahn tests of the blood gave negative reactions. Quantitative intracutaneous tests with K.O.T. 1:1000, 1:10,000, 1:100,000, 1:one million, 1:ten million, and 1:one hundred million showed elevated, red, edematous papules ranging from 2 cm. to 0.5 cm. in diameter respectively, surrounded by a less inflamed but edematous halo.

A small piece of skin containing several papules was removed from the abdomen for microscopic examination. The patient refused to allow a sufficient amount of skin to be taken for guinea pig inoculation.

A section (Fig. 2) of a papule stained with hematoxylin and eosin shows an inflammatory reaction confined entirely to the papillary region. In the intact epidermis above, the horny and granular layers are normal. The prickle cell layer is reduced from the normal thickness of four to six cells, to from two to

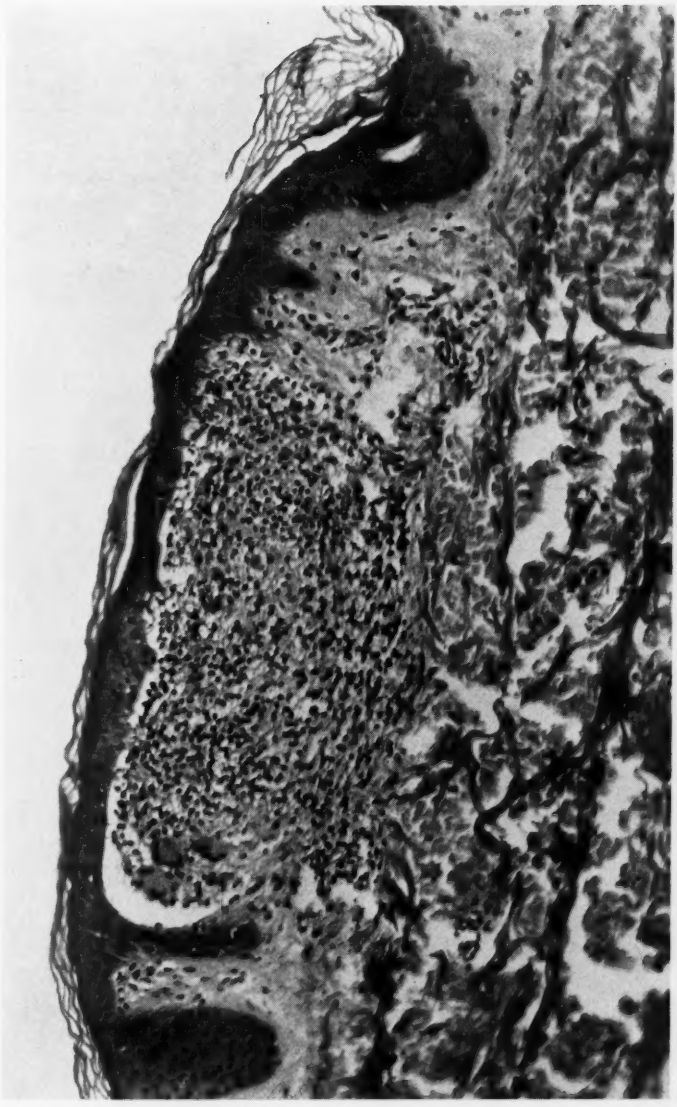


FIGURE 2: Case I. An interfollicular papule of lichen nitidus. Note the position of the granuloma in the papillary layer and giant cells. (x 150).

three cells, and the germinal layer is obliterated. The granuloma is flat, sharply circumscribed, and delimited on each side by a cresenteric rete peg. It consists of edematous connective tissue in which a dense round cell infiltration is imbedded.

The architecture of the connective tissue and papillae is destroyed. A section stained for elastic tissue shows no elastic fibers in the inflammatory nodule. There is proliferation of fixed tissue cells; and a few epithelioid cells and proliferating capillaries are present. There are no eosinophils and only a few polymorphonuclear cells in the infiltrate. In the upper half (mostly the upper third) of the granuloma, there are a number of scattered cells containing melanin granules. In the left side of the granuloma, closely approximated to the epidermis, are three giant cells. In another section of a papule, a giant cell appears to lie almost wholly within the epidermis. The cytoplasm is completely filled with melanin granules. In sections of papules stained with a silver reducing stain, the pigment containing cells appear to be of two types: (1) cells resembling the chromatophores of irregular shape and containing coarse melanin granules as seen in normal papillae, and (2) cells containing fine melanin granules, resembling the basal cells of the epidermis.

In the corium and neighborhood of the granuloma, there is perivascular round cell infiltration of the same type and size as the round cells in the granuloma. The blood vessels are dilated but none shows endothelial proliferation. The deep corium and the subcutaneous tissue are normal.

In order to determine the relative efficacy of roentgen therapy and of an ointment containing 4 per cent each of salicylic acid and resorcinol in petrolatum[4], the lesions on one half of the body were given eight superficial roentgen ray treatments of 75 r at weekly intervals, while to the lesions on the other half of the body, the ointment was applied twice daily for the same period of time. After the fifth roentgen ray treatment, the papules were reduced to a glistening scale-less macule. After the eighth treatment, the macules had almost disappeared.

During the eight weeks of treatment with the ointment, the papules remained unchanged, although the skin showed some keratolytic effect. This half of the cutaneous surface is being treated with roentgen ray therapy at the present time and the eruption is disappearing.

Case 2: A white woman, twenty-seven years of age, came to the Clinic on March 3, 1939, complaining of an eruption on her arms which had been present since December, 1938. It appeared first in the cubital fossae and rapidly spread distally over the volar surfaces of the forearms to the wrists. At times the eruption itched slightly. She was disturbed by the fact that, when her arms were in a dependent position, the eruption became bright red. In January, 1939, the eruption appeared in a few places on the abdomen.

There was no relevant family history of chronic diseases, and she had never been exposed to, nor had any symptoms or examinations relative to tuberculosis.

Physical examination showed a well developed and well nourished young woman of sthenic habitus. A roentgenogram of the chest showed no evidence of tuberculosis. She presented ill-defined, irregular coin-sized areas of brownish-red color on the volar aspect of the forearms, wrists, and one patch on the left arm near the anterior axillary fold (Fig. 3). A large patch occupied all of each cubital fossa. These patches were made up of numerous discrete, uniformly pinhead sized, flat brownish-red to skin colored papules. Some of the papules were polygonal but under a magnifying glass this was seen to be due to the lesions being situated at intersections of the cross markings of the skin. Others showed a slight scale and a tiny central depression. Most of the scaly papules, relatively few in number, were perifollicular. However, most of the papules were round, smooth, and glistening. Similar groups of papules were on the abdomen and dorsa of the feet. The rest of the cutaneous surface and the buccal mucous mem-

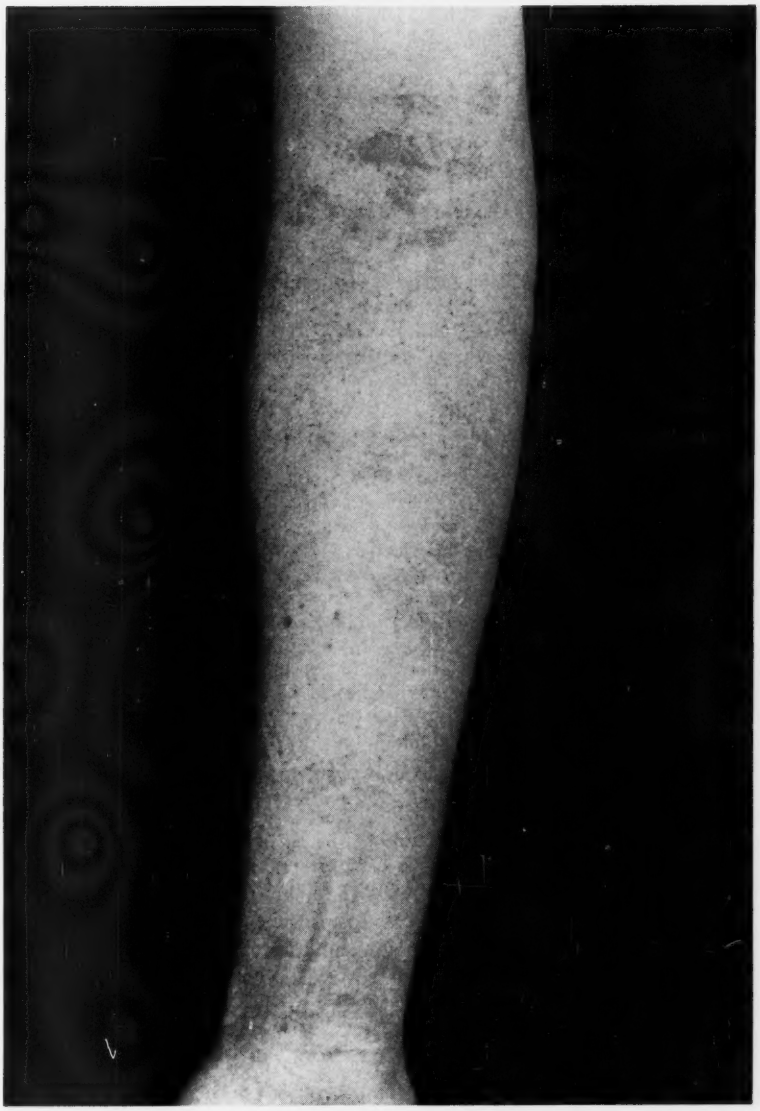


FIGURE 3: Case 2. Lichen nitidus.

brane showed no eruption. On diascopy, the papules were seen to be granulomatous.

The hemogram and urinalysis were normal. The fasting blood sugar level was 88 mg. per 100 cc., and Wassermann and Kahn tests of the blood gave negative

reactions. Intradermal tests with K.O.T. 1:100 showed a 2 plus reaction, while 1:10,000 and 1:100,000 were negative.

A small piece of skin containing several papules was excised from the left forearm for microscopical examination. A section containing a perifollicular papule (Fig. 4) surrounding a hair follicle shows an inflammatory reaction, the greater part of which is on the right side of the follicle. On both sides of the shaft, the granuloma extends downward past the mouths of the sebaceous glands to a point where the shaft disappears from the section. Except for the downward prolongation along the follicle, the inflammatory reaction is confined to the papillary layer and sharply limited at the upper part of the corium. The epidermis above is intact. That part of the horny layer above the summit of the granuloma shows parakeratosis, below which the granular layer is absent. On either side of the parakeratosis, where the epidermis regains its normal appearance, the horny layer shows moderate hyperkeratosis and the cells of the granular layer reappear. There is a small hyperkeratotic plug in the follicle. The prickle cell layer is reduced to two or three cells in thickness while the germinal layer is obliterated by invading round cells.

The granuloma is roughly spherical, consisting of a small round cell infiltrate slightly more dense at the periphery, and made up of uniform size and type of cells. No polymorphonuclear leukocytes, eosinophils or plasma cells are present. The infiltrate is nested in an edematous connective tissue stroma with proliferating fixed tissue cells. At the very summit of the granuloma, there is a giant cell containing twenty-five nuclei, beneath which is what appears to be the remains of a rete peg, the continuity of whose cells is disrupted by the infiltrating round cells. There is an increased number of new formed capillaries. In the upper corium, there is perivascular round cell infiltration of the same type of cells as those in the granuloma. There is no endothelial proliferation but the blood vessels are dilated. The deep corium and subcutaneous tissue appear normal. Other inflammatory nodules in the papillae are identical with the one just described except for an absence of parakeratosis, hyperkeratosis, and giant cells. No pigment containing cells, except for a few chromatophores in the normal papillae, is seen in this or other sections studied.

The eruption was treated with five superficial roentgen ray treatments of 75 r each at weekly intervals. After the fourth treatment, the papules had almost disappeared. When seen a year later, the patient stated that within two weeks following the last treatment, the eruption disappeared entirely and has not recurred. A thorough examination of the skin showed no evidence of the eruption.

Briefly, the histologic characteristics of the papules in these two cases are of a sharply circumscribed granuloma, which has invaded and destroyed the basement membrane, germinal layer, and part of the prickle cell layer, limited to the papillary region. In young lesions, the granuloma is limited to a single papilla. Giant cells of the foreign body type may be found in most of the older lesions. The granulomas consist of edematous connective tissue stroma, proliferating fixed tissue cells, and a rather dense but evenly distributed small round cell infiltration. They may be situated on one side, or occasionally may surround a hair follicle. In a typical lesion, the inflammatory reaction is limited on either side by a somewhat crescentric and prolongated rete peg. Newly formed capillaries growing into the granulomas frequently are seen in older lesions.

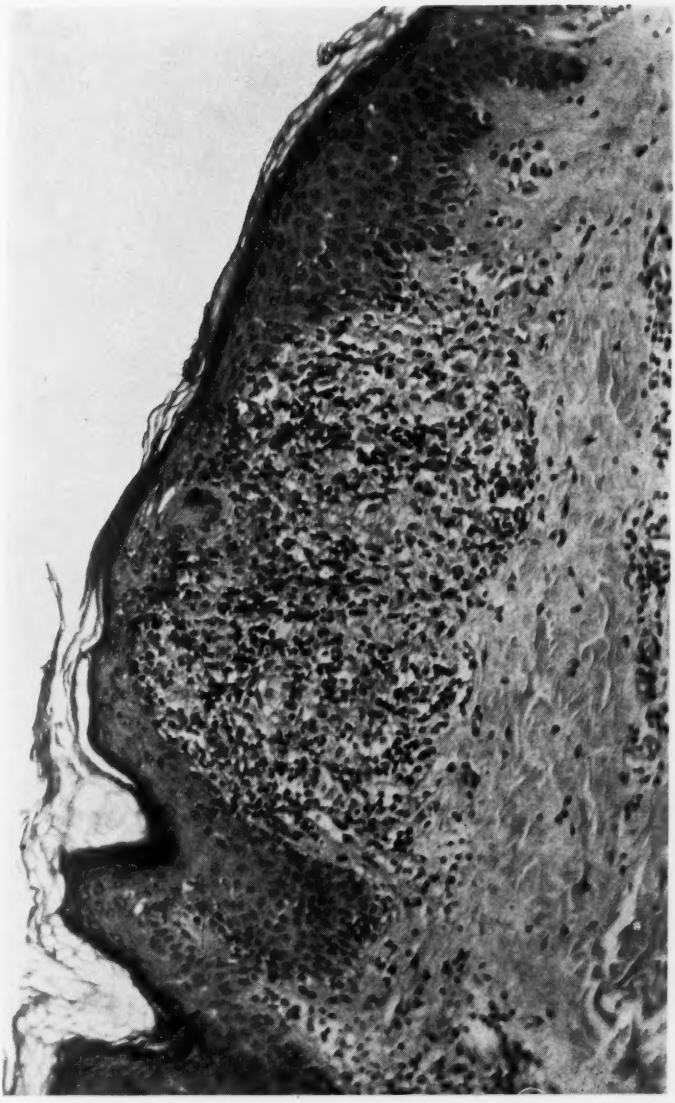


FIGURE 4. Case 2. Perifollicular lichen nitidus papule showing only that part on one side of a follicle. Note the giant cell lying almost wholly within the epidermis. (x 150).

McCarthy[15] mentions pigmentation of giant and other cells in the cells in the granuloma. Trimble and Maloney[16] did not mention this finding in their two patients who were negroes. The position of the giant cells

FIGURE 5: A mature lichen planus papule. Note the position of the infiltrate in the papillary layer and corium in contrast to figures 2 and 4. (x 150).

and the small melanin granules in their cytoplasm in Case 1 suggests that they could be of epidermal origin. The large number of cells in the upper part of the granulomas containing fine granular melanin are

morphologically similar to basal cells. In contrast, the more deeply situated irregular shaped cells which contain coarse melanin granules are morphologically identical with chromatophores in the normal papillae.

Diagnosis

In Case 1 the history of intimate exposure to tuberculosis, a high degree of skin sensitivity to tuberculin, and the presence of giant cells in the papules suggested a relationship between the eruption and tuberculosis. On the other hand, a positive tuberculin reaction is common in adults who show no evidence of tuberculosis in the anamnesis and/or on repeated examinations as in this case. The lack of histologic evidence for the lesions being tuberculous has been discussed above. Although it was not possible to obtain tissues for animal inoculations or to make exhaustive studies of serial sections for acid-fast bacilli, the negative results recorded in the literature would seem to indicate that these procedures in this case also would have given negative results. A search for tubercle bacilli in a few microscopical sections gave negative results.

As for the cutaneous manifestations of tuberculosis, including the tuberculids, lichen scrofulosorum more closely resembles lichen nitidus. However, the former usually occurs in children with frank tuberculosis, while lichen nitidus is generally seen in adults, usually without evidence of tuberculosis. The eruption of lichen scrofulosorum tends to group and is decidedly scaly and perifollicular with spreading borders made up of the papules and clearing centers. Only a few of the papules of lichen nitidus are perifollicular (none were found in this case). When the papules become so closely aggregated in scaly patches, they usually retain their individuality and the patches have not been observed to clear in the center.

Histologically, lichen scrofulosorum presents a variable picture with an almost entire dissemblance to a typical tubercle with central necrosis. Predominating is a perifollicular infiltrate containing many lymphocytes, few if any giant cells, and a few epithelioid cells. In the plane type usually occurring in the vicinity of the perifollicular type, the infiltrate is deeper in the corium than in lichen nitidus, does not infiltrate the epidermis, and is not so sharply outlined nor uniform as lichen nitidus. Tubercle bacilli have been found in the lesions of lichen scrofulosorum.

In Case 2, a small number of scaly perifollicular papules were interspersed between more numerous interfollicular papules, and the groups of lesions were not scaly. This patient presented no clinical evidence of tuberculosis and the histologic picture of the papules was characteristic of lichen nitidus. Aside from the presence of giant cells, the granulomas show no whorls of epitheloid cells or central necrosis. The rather dense round cell infiltration is evenly distributed. In a typical hard tubercle

of almost microscopic size, there is central caseation surrounded by concentrically arranged epithelioid cells which are in turn surrounded by lymphocytic infiltration. According to MacCallum[18], "There is absolutely no provision for a blood supply in such nodules (tubercle), and those capillaries which were present at that point before are found to be obliterated, so that if an organ studded with tubercles be injected through an artery with blue gelatin, each tubercle will stand out white against a blue background." New capillaries were seen in all the mature granulomas studied. Therefore, it seems that the typical well developed granuloma of lichen nitidus can readily be distinguished from a tuberculous nodule.

In these two cases it was not difficult to differentiate between the eruption present and lichen planus. In lichen planus, pruritus usually is pronounced, and both patients were reminded of the slight itching only when asked. In Case 2, the brownish-red color and vaguely polygonal papules might be confused with lichen planus papules of the same size, but, although the lesions of lichen nitidus are uniformly the same size, lichen planus papules vary in size from a millet seed to a small pea, and the larger lesions have a distinct lilac to purplish color. Although both eruptions tend to groupings of the papules, in lichen nitidus the papules retain their individuality while in lichen planus they coalesce to form figures. The white lines or dots (Wickham's striae) in lichen planus papules are not present in lichen nitidus. Lichen planus rarely, if ever, presents an involvement of the penis as does lichen nitidus (Fig. 1), but often occurs on the glans with the formation of annular lesions. Lichen nitidus is rare in the mouth while a lichen planus involvement of the mouth is common. Lichen planus, on involution, usually leaves pigmentation which may persist for months, but lichen nitidus leaves no trace.

Histologically, very small lesions of lichen planus may resemble lichen nitidus, but in well developed lichen planus papules there is no resemblance (Compare Figs. 2, 4, and 5).

Verruca plana juvenilis offered the least difficulty in the diagnosis as the papules have a warty surface which is easily removed with a curette while lichen nitidus papules have to be picked out. The verrucae vary in size and in color from light to dirty brown, and are less sharply defined.

Treatment

Several types of treatment have been used with success. In Sutton's case[4] the lesions disappeared following the use of salicylic acid and resorcinol (See Case 1). Niles successfully used gold sodium thiosulfate in increasing doses from 25 to 100 mg. in his case. Fox[16] and MacKee[17] caused the eruption to disappear with superficial roentgen therapy.

Summary and Conclusions

Two cases of lichen nitidus are reported with a description of the clinical and histologic features. In one case, an unusual finding of melanin in giant and epithelioid cells is described. The clinical and histologic differences between lichen nitidus, cutaneous tuberculosis, and lichen planus are pointed out; and, in the absence of the known cause, it is concluded that lichen nitidus is not related to the latter two diseases. In both cases the eruption disappeared after five to eight roentgen ray treatments, and in one case, which has been under observation for fourteen months, the eruption has not recurred.

References

1. Pinkus, F.: Uber eine neue Knötchen formige Haut Eruption, Behandl. der Berlin Dermat. Gesellsch., 12:85:11, 1907.
2. Arndt, G.: Beiträge zur Kenntnis des Lichen Nitidus, Dermat. Ztschr., 16:551, 1909.
3. Kyrle, J. and McDonagh, J. E. R.: Lichen nitidus, Brit. J. Dermat., 21:339-346, (November) 1909.
4. Sutton, R. L.: Lichen nitidus, J. Cutan. Dis., 28:597-605, 1910.
5. Civatte, M. A.: Lichen nitidus coexistant avec un lichen plan, Bull. Soc. Fr. de derm. et syph., 22:65-67, 1911.
6. Niles, H. D.: Lichen nitidus; report of case treated with gold sodium thiosulfate and review of literature, Arch. Dermat. & Syph., 22:687-697, (October) 1930.
7. Chatellier, L.: Sur la tuberculide licheniforme et nitida, Ann. de derm. et syph., 7:340-351, 1918-19.
8. Gougerot, H. and Burnier, H.: Un cas de "lichen nitidus" generalise gueri par la tuberculinotherapie, Bull. Soc. Fr. de derm. et syph., 41:650-652, (April) 1934.
9. Barber, H. W.: Discussion on a case of lichen nitidus presented by K. Sibley, Brit. J. Dermat. & Syph., 43:136-138, 1931.
10. Dowling, C. E.: Discussion on a case of lichen nitidus presented by K. Sibley, Brit. J. Dermat. & Syph., 43:136-138, 1931.
11. Haynes, H. and Hellier, H.: Lichen nitidus associe a du lichen plan et a de la lichenification verruqueuse, Ann. de dermat. et syph., 8:192-214, (March) 1937.
12. Ellis, F. A. and Hill, W. F.: Is lichen nitidus a variety of lichen planus? Arch. Dermat. & Syph., 38:569-573, (October) 1938.
13. Michelson, H. E.: Lichen nitidus, Arch. Dermat. & Syph., 7:763-772, (June) 1923.
14. Barber, H. W.: Lichen nitidus, Brit. J. Dermat., 38:143-156, (April) 1926.
15. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby, 1931.
16. Fox, H.: Discussion: Trimble, W. B. and Maloney, E. R.: Lichen nitidus, Arch. Dermat. & Syph., 7:452-461, (April) 1923.
17. MacKee, G. M.: X-rays and Radium in the Treatment of Diseases of the Skin, Philadelphia, Lea and Febiger, p. 744, 1938.
18. MacCallum, W. G.: A Textbook of Pathology, 4th ed., Philadelphia, W. B. Saunders Co., p. 606, 1928.

PERORAL USE OF METHYL TESTOSTERONE IN TESTICULAR DEFICIENCY

E. PERRY MCCULLAGH, M.D.

The effects of androgenic hormone therapy have been studied rather completely within the past few years, not only in testicular deficiency but also in such conditions in women as menorrhagia, the climacteric, and for the inhibition of lactation.

In eunuchoidism or eunuchism the typical effects of androgens include increase in libido sexualis, in potence, energy, growth of the external and internal genitalia, stimulation of growth of secondary sexual characteristics, and if the dose is sufficient, the rate of epiphyseal closure increases. Where sperms are present, continued large doses of testosterone propionate tend to suppress their production. In addition, there are certain metabolic effects which include retention of sodium, chloride, nitrogen, and water, with an accompanying gain in body weight[1]. There is evidence also that some elevation of the basal metabolic rate exists, although to date this is less definite.

Most striking clinical effects have been produced by the intramuscular use of testosterone propionate in oil in doses approximating 10 to 50 mg. a day or on alternate days. Apart from depression of sperm production[2] and the possibility of too rapid epiphyseal closure, no harmful effects of consequence have been reported. In women, production of masculinization is an obstacle to its free use.

The evidence that good clinical results can be obtained by percutaneous administration of androgens is not impressive. Vest[3] has shown clearly in cases of eunuchoidism that excellent results can be obtained by the subcutaneous implantation of pellets of testosterone. Foss[4] reported the successful clinical use of peroral methyl testosterone. The results were comparable to those reported by us[5] and others in cases of testicular deficiency treated with injections of testosterone propionate.

Since January, 1940, we have observed some clinical effects of methyl testosterone given orally in nineteen cases of various types of testicular failure and impotence and in a few cases of women. It is not advisable at this time to make a complete comparison of these results with those of cases treated with testosterone propionate. It is evident, however, that the drug is very effective and that its effects appear to differ in some ways from those of testosterone propionate.

Methyl testosterone has been given to our cases in tablets containing 25 mg. each. In most instances a dose of 25 to 75 mg. per day has been employed and in a few cases as much as 150 mg. a day has been given. Such treatment has been well tolerated in all cases, and there have been no gastro-intestinal disturbances.

In cases of testicular deficiency, either with obvious clinical signs or in those few in which the diagnosis was accepted on the basis of symptoms and low androgen assays, the response to this treatment was approximately the same as that seen following injections of testosterone propionate. Within a few days there occurred a striking increase in the number and power of penile erections, and a sense of energy and well being was noted. These symptoms usually disappeared within a week after discontinuing the drug. After several weeks of treatment there was a measurable increase in the size of the penis, and an increase in the amount of pubic and axillary hair. In one case lowering in the pitch of the voice was noted after two months of therapy. In another, a distinct increase in the size of the prostate could be detected after four months of treatment.

In patients who previously had had injections of testosterone propionate over many months, it was judged that the symptomatic effect of a certain amount of testosterone propionate could be reduplicated by approximately three to four times the amount of methyl testosterone by mouth. In several cases it was noted that the striking sexual stimulation which occurred within a few days tended to diminish after several weeks, while the same dosage continued to be used. A similar diminution of effect has been noted from continued doses of diethyl stilbestrol in women (Schorr and Papanicolaou). Whether this may be connected with an increasing power on the part of the liver to metabolize the drug, as has been suggested for diethyl stilbestrol, is unknown. On ingestion of methyl testosterone, gain in body weight has been a prompt and rather striking feature in some cases. On doses of 75 mg. a day, weight gains on the order of ten pounds in two weeks have been seen. One man voluntarily discontinued taking the drug because of an uncomfortable sense of bloating, associated with a gain of thirteen pounds in weight in twenty-three days. In another case, a similar gain in weight was associated with severe headache. In this instance treatment was being given for hypogonadism incident to a pituitary tumor which had been operated upon within the preceding month, and it was suspected that the headache was caused by an increase in intracranial edema. Such increases in body weight suggest that the effect of methyl testosterone on sodium, chloride, and water retention is similar to that seen following the use of testosterone propinate and other related steroids.

Studies of excreted androgens following the oral administration of methyl testosterone indicate that in the body the metabolism of this material differs materially from that of injected testosterone propionate. In the case of the latter drug, it has been shown that the symptomatic response in hypogonadal males is associated with a rise of urinary androgens to approximately the range of normal. Single injections of 10 mg. of testosterone propionate into eunuchoid men cause an increase

in excreted androgens varying from 10 to 20 international units in twenty-four hours. Following injection of 50 mg., 60 to 100 units is excreted in twenty-four hours[6]. This sequence does not appear to take place with methyl testosterone. Following administration of amounts of methyl testosterone sufficient to give a decided symptomatic response, little or no rise in urinary androgens can be detected by the capon assay method of McCullagh and McLin[7].

In cases observed to date, methyl testosterone seems to have a definite effect in causing an elevation of the basal metabolic rate. This is illustrated in the case reported below. Each basal metabolic rate listed is an average of two runs. The Sanborn graphic apparatus was used and the Aub-Dubois standards were employed.

Report of Case

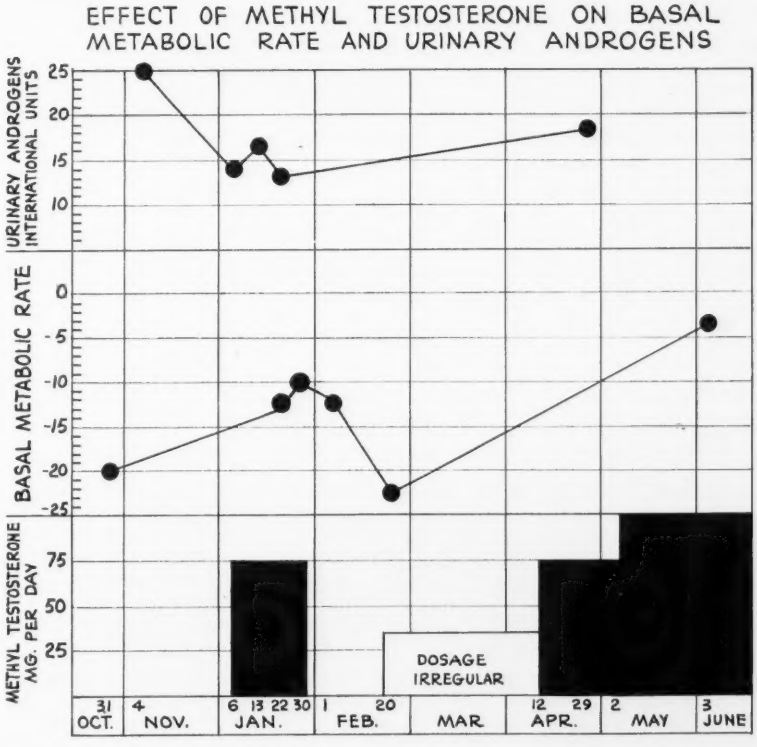
A man, twenty-eight years of age, was examined in September, 1939. At the age of fourteen years, severe trauma to both testes had been followed by marked swelling. Repeated trauma to both glands occurred six months later and this was followed by complete disappearance of the testes, so far as the patient could determine. The voice had changed somewhat prior to that time. Following the second injury, there was little or no further development of pubic and axillary hair or genital growth. Secondary sex characteristics, such as the beard, did not appear. He married when twenty-five years of age. He had little or no sexual desire and coitus was possible, occasionally with orgasm but without ejaculation. There were no signs suggestive of pituitary disease or hypothalamic injury. He had no cold intolerance, no dryness of the skin, hair, or nails, and no edema or paresthesiae. He was 70¾ inches tall, with a span of seventy-two inches and he weighed 188 pounds. The facial appearance was boyish. The skin was very fine in texture, and there was no beard. The pubic and axillary hair was sparse and there was virtually no hair on the trunk or extremities. The penis measured 10 cm. in length from the pubic bone to the tip. The scrotum was very small and no testes were palpable. The prostate gland was minute, its borders being defined with difficulty by rectal palpation.

Wassermann tests of the blood gave negative reactions. Other laboratory tests were not significant, except those listed below. Blood cholesterol determinations done in October, 1939, and in February, 1940, were 222, 208, and 194 mg. per 100 cc. A roentgenogram of the skull indicated no enlargement of the sella turcica, and all the epiphyseal lines were closed. A modified Friedman test showed no measurable gonadotropic substances.

A diagnosis of eunuchoidism of moderately severe degree following testicular trauma was made.

The treatment was as follows: For twenty-three days he received 25 mg. of methyl testosterone given orally in tablet form three times a day. Within a day or two, erections, which had occurred once a week or less, were occurring daily. After two weeks erections were occurring almost constantly. The patient noted considerable fullness of the tissues of the body and a sense of bloating. In twenty-three days his weight had increased to 213¾ pounds, a gain of 13¾ pounds. Treatment was discontinued and no methyl testosterone was taken from January twenty-ninth to April twelfth. Following the discontinuance of treatment, sexual stimulation disappeared in about a week and the patient noted that he had less energy. Twenty days after discontinuing treatment, his weight had

fallen to 209 pounds. From April twelfth to May twenty-second methyl testosterone was given in doses of 25 mg. three times a day. Again there was a marked increase in sexual power within four days after beginning treatment. After this had been continued for several weeks, a gradual diminution in the sexual stimulation occurred, and thirty-nine days after beginning treatment (May 21), erections were occurring about normally but there was no excessive stimulation. His weight had fallen to as low as 201 pounds on the second of May and rose again to 209 on May twenty-first. By the twenty-first of May certain anatomical changes had taken place. There was some growth of the penis. On June fifth the penis was 15 cm. in length and much increased in diameter. The prostate was distinctly larger than on the original examination, having increased from perhaps one quarter to three quarters of normal size. The patient still noted an increase in the sense of energy as compared to the period prior to the treatment. On June fifth he weighed 214 pounds.



Repeated estimations of the basal metabolism indicate that methyl testosterone has a distinct effect upon the basal metabolic rate. On October 31, 1939, the basal metabolic rates averaged minus 20 per cent. After having had treatment as listed above for twenty-four days, the basal metabolism was minus 12 per cent. The following day it was minus 10 per cent. On February first it was minus 12 per cent. After having had no treatment for twenty-two days, the basal metab-

olism was minus 23 per cent. No thyroid therapy had been used throughout. The drug was then used in the doses indicated on the chart. The basal metabolism was minus 4 per cent on June third, following doses of 100 mg. per day.

Assays for urinary androgens were equally interesting. Before any treatment was given, bio-assay by the method of McCullagh and McLin[7] showed 25 international units on November fourth. An assay of this height has been seen occasionally in hypogonadal individuals, and, although it is not the rule, it undoubtedly represents definite quantities of androgens. These almost certainly arise from the adrenal cortex and do not represent testicular hormones. On January sixth, prior to the beginning of treatment, repetition of the bio-assay showed 14 international units. Assays in normal individuals by this method show between 18 and 80 international units of androgens. Treatment was begun on January sixth and one week later, when striking clinical effects were obvious, bio-assay revealed 16 international units of androgens, and one week subsequently, when sexual stimulation was excessive, bio-assay had still shown no rise whatever, showing 13 international units. On April twenty-ninth, following consistent use of 75 mg. of the drug daily, bio-assay revealed only 19 international units of androgens. As mentioned above, such a complete lack of response, so far as can be determined by the measure of excreted androgens, is entirely different from that which we have seen following the use of testosterone propionate, and indicates clearly that the metabolism of this substance in the body differs from that of testosterone propionate.

Summary

Oral methyl testosterone is effective therapy in eunuchoidism. In terms of clinical symptoms its effectiveness as compared to testosterone propionate injections approximates 3 or 4 to 1.

The metabolism of methyl testosterone differs from that of testosterone propionate in that clinically effective doses of the propionate are followed by a rather marked increase in urinary androgens. With methyl testosterone, this sequence does not occur to the same extent.

Methyl testosterone has the power to raise the basal metabolic rate.

An illustrative case is reported.

References

1. Kenyon, A. T., Sandiford, I., Bryan, A. H., Knowlton, K., and Koch, F.: Effect of testosterone propionate in eunuchoidism, Proc. Soc. Exper. Biol. & Med., 37:683-685, (January) 1938.
2. McCullagh, E. P. and McGurl, F. J.: The effects of testosterone propionate on epiphyseal closure, sodium, and chloride balance and on sperm counts, Endocrinology, 26:377-384, (March) 1940.
3. Vest, S. A. and Howard, J. E.: Clinical experiments with androgens; method of implantation of crystalline testosterone, J.A.M.A., 113:1869-1872, (November) 1939.
4. Foss, George: Oral application of methyl testosterone and its simplification of androgen therapy, Brit. M. J., 2:11-12, (July) 1939.
5. McCullagh, E. P.: Treatment of testicular deficiency with testosterone propionate, J.A.M.A., 112:1037-1044, (March) 1939.
6. McCullagh, E. P.: Rumsey, J. M., and Cuyler, W. K.: Excretion of urinary androgens following injection of testosterone propionate, Endocrinology, 24:833-837, (June) 1939.
7. McCullagh, D. R. and McLin, T.: Extraction of androgens from urine, Endocrinology, 22:120-121, (January) 1938.

TREATMENT OF BLADDER TUMORS* A COMPARISON OF RESULTS IN PEDUNCULATED AND INFILTRATING TYPES

A Report of 130 Cases

E. E. FERGUSON, M.D.

INTRODUCTION

Tumors of the urinary bladder have been, and still remain, one of the most difficult problems of urology, particularly in the selection of proper treatment. My purpose is to show the value of the cystoscopic interpretation of a tumor as a criterion for the selection of treatment.

At the Cleveland Clinic, bladder neoplasms constitute about 4 per cent of all malignancies, and 35 per cent of all cases of malignant diseases of the genito-urinary tract. Of 512 cases of bladder tumor treated over a twenty-year period, only forty-five patients (8.7 per cent) survived for more than five years.

The 130 cases in this review were selected at random from a total of 160 cases seen at the Cleveland Clinic from 1931 to 1939. Thirty cases are not included because of the meagerness of clinical data. Prior to this relatively short period of years, cystoscopic interpretation did not receive the present emphasis, and transurethral excision of bladder tumors with the resectoscope, used extensively in our series of cases, was unknown.

Sarcoma of the bladder, which occurs in less than 1 per cent of the cases, and other rare forms of bladder tumor are not discussed in this report.

CLASSIFICATION

The majority of bladder tumors are epithelial in origin and papillary in form. All papillary tumors are considered as potentially malignant.

For clinical interpretation, bladder tumors are classified as pedunculated or infiltrating. Pedunculated tumors which may be single or multiple are villous growths surmounted on a stalk growing out from the pedicle. Infiltrating tumors are broad based, sessile, nodular or papillary, ulcerated growths, with evidence of invasion of the bladder wall. Little attempt is made to differentiate clinically the papillary from the more strictly infiltrating carcinoma, since both are malignant neoplasms necessitating radical treatment.

It is not within the scope of this paper to discuss the histology of bladder tumors. Dr. Allen Graham, of the Department of Pathology, in accord with the clinicians, bases his classification on the presence or

*Abstract of thesis which was awarded the William E. Lower Fellowship Thesis Prize for 1939.

absence of infiltration of the bladder wall. A classification which we tend to follow is given below.

A. Papillary
   1. Non-infiltrating
      a. Benign papilloma
      b. Malignant papilloma
   2. Infiltrating
      a. Papillary carcinoma
      b. Infiltrating carcinoma

B. Non-papillary
   1. Infiltrating
      a. Squamous cell carcinoma

Graham believes that grading the tumors according to their cellular differentiation is the best index of the inherent malignancy of the tumor. A grouping, combining the cystoscopic appearance, physical findings, and histologic examination, would be more practical.

In 75 per cent of our cases, the neoplasm involved the dependent portion of the bladder. In papillomas found in aniline workers, and in papillomas produced experimentally in dogs, the tumors occurred in that portion of the bladder in which urine collects, which supports the theory of a urogenous mechanism in the production of tumors.

In support of chronic irritation as a causative factor, one of our cases developed a carcinoma in a preexisting area of leukoplakia. Another case developed an infiltrating carcinoma at the seat of a lesion said to be a Hunner ulcer by the referring physician.

Fifty-five per cent of the cases of papilloma occurred in patients between sixty and eighty years of age. Seventy per cent of the cases of carcinoma were discovered in patients between the ages of fifty and seventy years. No case of malignancy was noted before the fourth decade, and only 7 per cent before the fiftieth year. Tumors in men outnumbered those in women three to one.

Symptomatology

In all but thirty cases of bladder tumor, hematuria was the first symptom. Only seven patients related that there had been no blood in the urine; 37.6 per cent of the patients presented themselves more than one year following the initial bout of hematuria, which, in a number of cases, had been followed by a free interval for as long as three years. We found no characteristic features regarding the quantity or quality of the blood which in itself is diagnostic of bladder tumors.

When frequency appears before hematuria, the growth is usually near or at the bladder neck. Other urinary disturbances such as dysuria, hesitancy, intermittency, and sudden painless stoppage of the urinary stream, were occasionally present when the tumor occurred at the internal vesical sphincter. Pain and loss of weight or other constitutional

symptoms appear quite late in the course of bladder tumors and then only in cases with extensive infiltrating carcinoma. Although obstruction of the vesical portion of the ureter was noted in 7 per cent of our cases, rarely were any subjective symptoms produced.

Diagnosis

Cystoscopy is essential for the early diagnosis of vesical neoplasms. On occasion, however, roentgen examination, biopsy, and physical examination, in order of value, supply the examiner with more direct information than does the cystoscope. We place great stress upon the value of the cystoscopic and cysto-urethroscopic examination, which determines the size, character, and attachments to the bladder after the tumor is discovered. After a thorough search for other tumors, an effort is made to classify the lesion as either pedunculated or infiltrating.

Cystography and excretory urography are next in value to the cystoscope. The excretory urogram has two distinct advantages over the cystogram: (1) With the use of the excretion method, serial cystograms afford a better view of the location and type of tumor than does the single cystogram. A 5 per cent solution of sodium iodide, the media used in the cystogram, is so intensely radio-opaque that a filling defect may not be discernible. Diodrast, utilized in excretory urography, is less dense and more readily reveals the filling defect. (2) The state of the upper urinary tract and of the kidney function, and the primarity of malignant papillomas of the renal pelvis, with implants in the bladder, also may be established by excretory urography.

The value of biopsy is limited to borderline cases, in which a closed method of radiation alone is contemplated previous to cystectomy.

Rectal or vaginal examinations, although valuable, will not give any information about pedunculated growths of average size. Its greatest value is in determining induration of the bladder wall and the degree of perivesical extension rather than in establishing the presence of a neoplasm.

Treatment

We have found it difficult to set down any hard and fast rules concerning treatment as each case is studied and treated individually. At the Cleveland Clinic, the type of therapy is determined largely by:

1. Cystoscopic classification
2. Position of the tumor
3. Size of the tumor
4. State of the upper urinary tract

The cystoscopic classification is of paramount importance. Table 1, in correlating the cystoscopic classification and the survivals, shows the value of this procedure.

TABLE 1
CYSTOSCOPIC CLASSIFICATION AND SURVIVAL

Time	*Pedunculated*	*Infiltrating*	*Total*
Less than one year	15	6	21
One to two years	6	3	9
Two to three years	6	1	7
Three to four years	4	2	6
Four to five years	6	2	8
Five to six years	4	1	5
Six or more years	7	2	9
Total alive	48	17	65
Dead	6	49	55
Lost	6	4	10
	60	70	130

The position of the tumor greatly influences the selection of the type of treatment. In our series, growths on the lateral wall comprised 50 per cent, and tumors on the trigone and bladder neck, 26 per cent of the total. The Carcinoma Registry Committee points out that only 23.4 per cent of the tumors on the lateral wall can be excised without interfering with the urethra or ureters. Only a very small percentage of our cases required reimplantation of the ureter.

The size of the growth may be the deciding factor between an open and closed procedure, and between the use of surgery alone or supplementary diathermy and radiation.

Kidney infections, with dilated ureters and kidney pelves, is a contraindication to a long radical procedure, and the proceeding with ureterosigmoidostomy. Before any radical operation is undertaken, roentgenograms of the chest, abdomen, and femurs should be negative. Metastases are more common in cases of bladder tumors than the average physician realizes.

Pedunculated tumors under 5 cm. should be treated by transurethral excision and fulguration. Fulguration alone practically has been discarded as a primary form of treatment, for with transurethral excision the tumor may be removed completely and thoroughly by one operation. Larger pedunculated tumors should be treated with cystotomy, excision, and fulguration of the base of the tumor. At this Clinic, the use of radium in the bladder has gradually decreased. The ulceration, increase in infection, and resulting symptoms offset any beneficial effect that the radium may give. High voltage roentgen therapy definitely will diminish the size and, in some cases, will destroy pedunculated tumors but will not prevent recurrence. In cases of multiple papillomas which are resistant to treatment, cystectomy should be considered. Table 2, in correlating the treatment of pedunculated tumors and survival, tends to substantiate the above beliefs.

TABLE 2

TREATMENT OF PEDUNCULATED TUMORS AND SURVIVAL

Type of Treatment	*Less than one year*	*1-2 yrs.*	*2-3 yrs.*	*3-4 yrs.*	*4-5 yrs.*	*5-6 yrs.*	*6 or more yrs.*	*With disease*	*No evidence of disease*	*Operative death within one month*	*Lost*
Excision and fulguration	1	1	1	1			3 1 malignant papilloma	1			
Excision and radon		1	1 papillary carcinoma	1		1	1		1		
Partial resection							1 papillary carcinoma				
Transurethral excision	8	4	2 1 papillary carcinoma	1	6	1		1		1	6
Fulguration	6		1	1		2	1		2		
Total 60											

Of the sixty cases of pedunculated tumors treated at the Clinic, twenty-one (35 per cent) have survived three years, and eleven (18.3 per cent) have survived five years. All but four of these tumors were considered to be histologically benign.

Nine patients were treated by cystotomy and simple excision, followed by fulguration of the base. Of these, five are living more than three years and four are living six years or more without evidence of disease.

Of the six patients treated with cystotomy, excision, and radon, three (50 per cent) survived more than three years and two are living more than five years.

One patient who had a partial resection of the growth has survived for six years without recurrence.

In thirty-one cases with pedunculated tumors, transurethral excision was the procedure of choice. Because the method has been in use here for only seven years, the number of five year survivals will be low. Twenty-nine patients are still alive, eight of these for more than three years and one for more than five years. There has been no recurrence of tumor in thirteen cases. In the ten patients in whom recurrences developed, a second transurethral excision controlled the lesion.

Endovesical fulguration was used in thirteen cases with three survivals at the end of five years. However, eleven still are alive and all are free of disease. Two died of other causes.

The problem of infiltrating tumors is much more difficult and, accordingly, deserves more radical treatment. If the tumor is on the movable portion of the bladder, it may be resected with a wide margin of normal bladder wall.

TABLE 3
TREATMENT, TYPE OF TUMOR AND SURVIVAL

Treatment	*Less than 1 year*	*1-2 years*	*2-3 years*	*3-4 years*	*4-5 years*	*5-6 years*	*6 or more years*	*Deaths*		
								With disease	*Operative death 1 month*	*Lost*
Excision		1 infiltrating carcinoma						1 infiltrating carcinoma		
Resection		1 papillary carcinoma	1 infiltrating carcinoma							
Cystectomy	2 infiltrating carcinoma	1 infiltrating carcinoma			1 papillary carcinoma			1 infiltrating carcinoma	2 infiltrating carcinoma 1 papillary carcinoma	
Bilateral ureterosigmoidostomy									3 infiltrating carcinoma 3 papillary carcinoma	
Excision and radon	1 squamous cell carcinoma 1 papillary carcinoma						1 papillary carcinoma 1 infiltrating carcinoma	1 papillary carcinoma 1 malignant papilloma 1 infiltrating carcinoma	1 malignant papilloma	1
Resection and radon								3 infiltrating carcinoma		1
Radon						1 infiltrating carcinoma		9 infiltrating carcinoma 1 papillary carcinoma 1 squamous cell carcinoma		1
Transurethral excision	2 infiltrating carcinoma			1 papillary carcinoma				1 infiltrating carcinoma 1 papillary carcinoma 1 squamous cell carcinoma	1 infiltrating carcinoma	1
Endovesical radon				1 infiltrating carcinoma						
X-ray								14 unknown		

Total 70

We have used fulguration by the loop and ball electrodes through a suprapubic incision, or radon only as palliative measures.

Cystectomy should be performed in tumors about the base or in large tumors involving the movable portion of the bladder, but not in an elderly or enfeebled patient. One should not wait until all other methods have failed and the patient has a hidden metastasis before advising cystectomy. In advanced cases, usually with dilatation of the ureters, renal infection, and impairment of function, less radical procedures are, of necessity, employed.

Table 3 correlates the treatment, type of tumor, and survival. Of the seventy cases of infiltrating tumors treated, seven (10 per cent) survived three years and three (4.2 per cent) survived five years or more. Only seventeen (24.1 per cent) of the total remain alive.

Of three patients having cystotomy and partial resection of the bladder, all are alive with one surviving more than three years.

Of two patients treated by cystotomy and excision of the tumor, only one is alive two years postoperatively.

Cystotomy with excision and implantation of radon seeds was used in nine patients. Of these, four are dead and two have survived five years without recurrence.

Of four patients treated with cystotomy, resection and interstitial radiation, three died with the disease and no report is available on the other.

Cystotomy with the implantation of radon seeds was the method of choice in thirteen patients. Eleven are dead. One five year survival was procured.

Of eight patients treated exclusively by transurethral excision, none has survived five years and but one survived three years.

Fourteen hopeless patients were treated by roentgen therapy and all are dead.

Of the 130 patients studied, twenty-eight (21.5 per cent) survived three years while fourteen (10.45 per cent) survived five or more years. In 1936, the Carcinoma Registry Committee reported a crude five year survival rate of 23 per cent. Fifty-five (42 per cent) of the total number of patients have died. The majority of the deaths were in cases with infiltrating carcinoma, of which forty-one (74.5 per cent) of the cases died within the first year. The chief cause of death was usually a severe infection in the bladder and kidneys.

Follow-Up

Operation constitutes only the first phase of the management. The patient should be warned of the marked tendency for bladder tumors to recur, and advised to come in at regular intervals for cystoscopic examina-

tion. Our routine is to have the patient come in three months after operation, and again three months later. If the bladder is clear in one year, yearly examinations are advised thereafter. Only by cystoscopic examination on each follow-up visit can small recurrences be recognized at a time when they can be destroyed easily.

Conclusions

1. The management of bladder tumors still offers many difficulties to the surgeon.

2. A cystoscopic classification of tumors, as pedunculated and infiltrating, based on the presence or absence of infiltration of the bladder wall, is offered. The classification is valuable in selecting the proper treatment and determining the prognosis. Pedunculated tumors offer a much more favorable prognosis than do infiltrating neoplasms. Eighty per cent of the patients with pedunculated tumors are alive as compared to 24.2 per cent with the infiltrating type.

3. All vesical neoplasms are potentially malignant.

4. The importance of painless, intermittent hematuria, the initial symptom in the majority of our cases, should be emphasized to the public; 37.6 per cent of our cases presented themselves more than one year following the initial bout of hematuria.

5. An effort has been made to demonstrate that no one method of treatment can be adapted to all cases.

6. Excellent results may be obtained by the transurethral excision of pedunculated tumors under 5 cm. in size.

7. Wide resection of infiltrating tumors is to be carried out whenever possible. Interstitial and external radiation has not controlled this type of neoplasm. Of twenty-eight patients treated by these methods, only two are alive. One has lived three years and the other five years.

8. Cystectomy should be done in less advanced and carefully selected cases. In the presence of upper urinary tract infection, cutaneous ureterostomy is the procedure of choice.

9. The majority of fatal cases die from severe bladder and kidney infection within a year. Rarely does one die a "cancer death."

10. Adequate follow-up examinations with the cystoscope are strongly advised.